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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : G06F 15/46	A1	(11) International Publication Number: WO 91/16683
		(43) International Publication Date: 31 October 1991 (31.10.91)

(21) International Application Number: PCT/US91/02786

(22) International Filing Date: 23 April 1991 (23.04.91)

(30) Priority data:
513,918 24 April 1990 (24.04.90) US

(71) Applicant: SCRIPPS CLINIC AND RESEARCH FOUNDATION [US/US]; 10666 North Torrey Pines Road, La Jolla, CA 92037 (US).

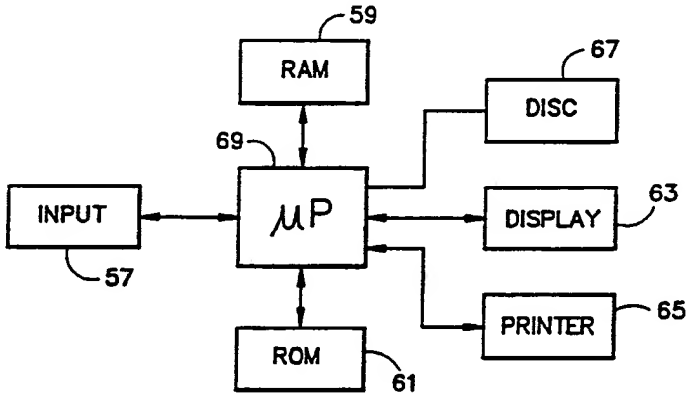
(72) Inventor: SKOLNICK, Jeffrey ; 744 Glen Arbor, Encinitas, CA 92024 (US).

(74) Agents: GAMSON, Edward, P.; Dressler, Goldsmith, Shore, Sutker & Milnamow Ltd., 4700 Two Prudential Plaza, 180 North Stetson Avenue, Chicago, IL 60601 (US) et al.

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.

(54) Title: SYSTEM AND METHOD FOR DETERMINING THREE-DIMENSIONAL STRUCTURES OF PROTEINS



(57) Abstract

The system comprises an input means (57) such as a keyboard for specifying (entering) selected amino acid sequences and other data such as temperature and fold preferences, a RAM (random access memory) (59) for storing such data, a ROM (read-only memory) (61) with a stored program, a CRT (cathode ray tube) (63) display unit and/or printer (65) an optional auxiliary disc storage device (67) for storage of relevant data bases, and a microprocessor (69) for processing the entered data, for simulating, under control of the stored program, the folding of the protein from its unfolded state to its folded (tertiary) state, and for displaying via the display unit (or printer) tertiary conformations of the protein in three dimensions.

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SYSTEM AND METHOD FOR DETERMINING THREE-DIMENSIONAL STRUCTURES OF PROTEINS

Background of the Invention

This invention relates to modeling systems generally, and particularly to computer-based simulation systems used in determining three-dimensional structures (tertiary native conformations) of globular protein molecules.

The value of determining structure or conformation of proteins is well known. For example, in 1961 a Nobel Prize was awarded to Max Perutz for his work in determining the structure of the hemoglobin protein in blood. From this discovery, we now understand more about sickle cell hemoglobin and how drugs can be designed to treat patients with this disorder.

The prediction of antigenic determinants also is based on the prediction of protein tertiary structure. One such scientific work is reported, for example, by Hopp and Woods in "Prediction of protein antigenic determinants from amino acid sequences", *Proceedings of the National Academy of Science USA* 78, pp. 3824-3828 (1981), and in "A Computer Program for Predicting Protein Antigenic Determinants", *Molecular Immunology* Vol. 20, No. 4, pp. 483-489 (1983).

The structure (native conformation) of the protein, particularly the conformation of the outer sites or sidechains (which are linked to the backbone and inner structures of the protein) often determines the capacity of the protein to interact with other proteins. One factor which directly influences conformation is protein folding. Deciphering the

rules through which the building blocks (amino acid sequences) of the protein affect folding promises significant improvements in the design of proteins, many with a host of new catalytic functions useful, for example, in the chemical, food processing, pharmaceutical, and other industries.

As a tool, computer systems are sometimes used to combine and display protein structures. One such system, used to convert two polypeptide chains to a single polypeptide chain, is described for example in U.S. Patent No. 4,704,692, entitled "Computer Based System and Method for Determining and Displaying Possible Chemical Structures for Converting Double- or Multiple-Chain Polypeptides to Single-Chain Polypeptides", issued November 3, 1987 to inventor Robert C. Ladner. Computer systems have also been used to investigate protein structures and predict protein folding. A few of such uses have been reported in *Protein Folding* by N. Go et al., pp. 167-81, ed. by N. Jaenicke, Amsterdam, Holland (1980); *Biopolymers* by S. Miyazawa et al., 21:1333-63, (1982); and *Journal of Molecular Biology,* by M. Levitt, 104:59-107 (1976).

These systems often (a) cannot process a full sequence of amino acid residues of a protein or protein segment (i.e., cannot process or otherwise represent the interactions of all the residues of the protein or protein segment; this task often becomes intractable, the system generally becomes unduly burdened by the many degrees of freedom of the residues), (b) cannot complete the folding process (because of inability of the system to recognize false, local energy - minima conditions), (c) cannot represent tertiary conformations in three dimensions, (d) cannot represent interactions between sidechains,

(e) do not display the pathway taken by a protein in folding, or (f) do not permit free (unconstrained) interactions between residues for more realistic simulation of real proteins.

What is needed and would be useful, therefore, is a computer-based system that would eliminate the above-mentioned deficiencies, and provide a faster way of determining protein structures, thereby increasing the productivity of many scientists and encouraging the undertaking of many more needed investigations, including investigation of structures of protein sequences obtained from mapping of the human genome.

Summary of the Invention

Accordingly, an improved computer-based system is provided that is capable of processing a full sequence of amino acid residues of a protein (e.g., plastocyanin), representing free (unconstrained) interactions between residues and between sidechains, tracking an entire folding operation (pathway) from the protein's unfolded (denatured) state to its fully folded (native) state, and displaying tertiary conformations of the protein in three dimensions.

The system comprises an input means such as a keyboard for specifying (entering) selected amino acid sequences and other data such as temperature and fold preferences, a RAM (random access memory) for storing such data, a ROM (read-only memory) with a stored program, a CRT (cathode ray tube) display unit and/or printer, an optional auxiliary disc storage device for storage of relevant data bases, and a microprocessor for processing the entered data, for simulating, under control of the stored program, the

folding of the protein from its unfolded state to its folded (tertiary) state, and for displaying via the display unit (or printer) tertiary conformations of the protein in three dimensions.

A novel lattice is employed for representing (framing) the various conformations of the protein as it folds from an unfolded sequence of amino acid residues to a tertiary structure. The model comprises a cubic arrangement of 24-nearest-neighbor lattice sites, with adjacent sites located a unit distance from each other, and adjacent α-carbons located a distance of $\sqrt{5}$ units from each other. The α-carbons represent a chain or backbone of the protein. Each α-carbon is shown to occupy a central cubic lattice side plus six adjacent cubic lattice sites defining a surface of interaction (e.g., an area or volume having a surface of finite size). Each sidechain is represented as being embedded in the lattice and occupying a selected number (four) of lattice sites located relative to the central site, the number of sites occupied by the sidechain being proportional to the number of sites defining the surface of interaction.

In response to specification of temperature and the amino acid sequence of the protein, the system determines the tertiary conformation of the protein using Monte Carlo dynamics with an asymmetric Metropolis sampling criterion. The system, (a) generates a three-dimensional representation of an unfolded conformation consisting of an α-carbon backbone and sidechains, (b) produces (in accordance with local conformational preferences of the residues, and the lowest total energy of interactions between close sidechain pairs which satisfies the criterion) successive likely conformations at the

temperature, according to the total energy of each conformation, (c) selects from the successive likely conformations the lowest total-free-energy tertiary conformation which satisfies said criterion, and (d) determines the coordinates of the selected tertiary conformation for display. In producing successive likely conformations, the system modifies each conformation by moving randomly selected residues (beads) and inter-residue bond vectors to different selected lattice sites by performing various type moves (single-bead jump-type moves, two-bead end-flip moves, chain-rotation type moves, and translation wave-type moves).

By the method employed by this system, simulation of protein folding and prediction of tertiary structure are not only performed with greater success and accomplished faster than by many existing methods, but the simulation itself becomes more manageable (tractable).

Brief Description of the Drawings

Fig. 1 is a diagramatic illustration of a globular protein in its native folded conformation.

Fig. 2 is a diagramatic illustration of a full sequence of amino acid residues of which the protein represented in Fig. 1 is comprised.

Fig. 3 is a block diagram of the system of the present invention.

Fig. 4 is a block diagram showing a perspective view of a cubic lattice model employed in the system of Fig. 3.

Fig. 5 is a block diagram showing a segment of a protein model comprising an α-carbon and sidechain in a cubic lattice of the type shown in Fig. 4.

Fig. 6 is a diagramatic illustration of an α-carbon backbone of a protein segment.

Fig. 7 is a diagramatic illustration of an α-carbon of the protein backbone segment shown in Fig. 6.

Figs. 8A-8C are diagramatic illustrations of selected simple arrangements of an α-carbon backbone and associated sidechains.

Fig. 9 is a diagramatic illustration of a jump-type move made by a randomly selected residue (bead) within the lattice of Fig. 4, effecting a change in conformation of the protein model.

Fig. 10 is a diagramatic illustration of a rotation-type move made by a pair of randomly selected bond vectors within the lattice of Fig. 4, effecting a change in conformation of the protein model.

Fig. 11 is a diagramatic illustration of a translation-type (wave-type) move made by a U-shaped segment within the lattice of Fig. 4, effecting a change in conformation of the protein model.

Figs. 12A-12D are diagrammatic illustrations of the folding of a selected segment of a protein to a β-barrel conformation.

Figs. 13A-13C are graphs showing an average number of native contact pairs between sidechains versus time.

Figs. 14A and 14B are graphical illustrations of a folding pathway defined by a sequence as it folds from an unfolded state to a folded (native) state.

Figs. 15A-15F are block diagrams (flow charts) showing a method employed by the system of Fig. 3 in simulating protein folding.

Fig. 16 is a block diagram showing an

alternate embodiment of the processor of Fig. 15.

Detailed Description of the Invention

A simplified representation of a globular protein (e.g., plastocyanin) in its native (natural, folded) form is shown in Figure 1. A simplified representation of a full sequence of amino acid residues of which the protein is comprised is shown in Figure 2. The protein becomes unfolded (denatured) when it is heated to an elevated temperature, and it refolds to its native form when the temperature is lowered to a selected level. Temperature may be specified in any unit (whether fahrenheit, centigrade, or Kelvin) and at any level or value (whether in or outside the transition range of the protein) as explained hereinafter. Generally, depending on the native biological conditions of the particular protein molecule being investigated, the temperatures that are specified are those in and bordering the transition region of the protein (typically, in and above 35°C-45°C).

Given a sequence of amino acid residues of a known or unknown protein, it would be useful, for example in the designing of a drug, to know to what protein form (structure, conformation) the sequence would fold if selected residues were changed (modified).

To determine the probable tertiary structure (three-dimensional conformation) to which a given sequence or modified sequence would fold, a simulation of the folding operation could be performed on a computer system of the type shown in Fig. 3. The system uses a "210" lattice model, as shown in Fig. 4. The system is described in detail hereinafter. Prior to description of the system,

however, to facilitate understanding of the invention, other aspects of the invention (such as lattice arrangement, types of movement of segments (residues) of protein within the lattice, orientational states of a segment, and inter-residue interaction) are described below.

Lattice Model, and Positioning of Protein Conformation

Referring now to Fig. 5, a section or segment **11** of a full sequence (e.g., a sequence of a protein much like that depicted in Fig. 2) is shown in stick form (without associated residues or atomic structure). The section **11** includes an α-carbon segment **13** and a sidechain (β-carbon) segment **15** representative of each amino acid residue of the protein.

The protein segments may be viewed as embodied within a cubic reference framework or lattice model (Fig. 4), constructed from vectors of the type (1,0,0), (0,1,0), (0,0,1), the distance between any two adjacent points being unity. The α-carbon atoms **13** when linked as shown in Fig. 6 form the backbone **14** of the protein. As shown in Figs. 4 and 7, each α-carbon **13** may be viewed as occupying a central cubic site **17** plus six adjacent cubic sites **18-23**, defining a finite surface of interaction. Adjacent α-carbon centers may be viewed as linked by a 210-type lattice vector **25**, as shown in Fig. 4.

The backbone **14** (Fig. 6) represents a structure of finite thickness about which a somewhat inflexible, hard core envelope of a chain of residues develop. The conformation of the backbone at the i^{th} α-carbon is specified in terms of $r^2_{\theta i}$, the square of the distance between adjacent α-carbons (i-1 and

α-carbons, and θ repr sents a bond angle that one of the α-carbons make with respect to the other, as shown in Fig. 6. In model units, the distance between consecutive α-carbons equals √5 units. Selected values of r^2_θ are 6, 8, 10, 12, 14, 16, and 18, expressed in model units, indicating various accessible bond angle states. These values represent internal orientational states corresponding to actual (known) physical conformations.

As shown in Figs. 5 and 8, each α-carbon has attached to it a sidechain 15, constructed for example in a helix conformation 27, or in a β-strand conformation 29. From the central vertex portion 31 of the α-carbon, the sidechain 15 is formed, comprising four lattice vector points (1,1,0), (1,1,0), (1,1,0), and (1,1,1) 33. Three points represent fcc-type (face center cubic) lattice vectors, i.e., vectors of the type (±1, ±1, 0). The fourth point represents a diamond lattice vector of the type (±1, ±1, ±1). This latter vector serves as the center of hydrophobic or hydrophilic interactions (explained hereinafter). The orientation of the sidechain depends on the backbone conformation, i.e., depends on r^2_θ. At least two of the three fcc vectors comprising the sidechain are shown in an L-conformation (i.e., with left-handed chirality). The diamond lattice-type vector is always shown in the L-conformation. (For a more detailed description of lattice rules which should be followed when constructing conformations, refer to Appendix A.) For the calculations described hereinafter, either the residues are glycine, in which case there is no sidechain, or the residues have a sidechain of uniform size.

Interactions Between Residues

The following is a description of how the 210 lattice model (Fig. 4) is used to denote interactions between elements (residues) of a given backbone conformation, and to denote the energy of such interactions. To specify the conformation of the backbone of a chain, composed of n residues on an α-carbon representation, n-2 bond angles (θ) and n-3 torsional angles (φ) must be specified. To determine the conformation of the first and last residues, a virtual residue is appended to each end of the chain. These virtual residues are represented as inert. They occupy space but are devoid of sidechains. Thus, with the addition of the two fictitious (virtual) residues, n bond angles and n-1 torsional angles can now be used to specify the backbone conformation of the chain. (For convenience in denoting segments, the residues of the chain may be numbered from 1 to n.)

With respect to expressing (representing) a preference for a given conformation, any intrinsic preference of the protein model for a particular conformation may be represented by the individual preferences of the respective residues for the various bond angle states. In the description that follows, the term local conformational preferences shall mean the relative preferences which each local group of residues (i.e., a selected residue plus two flanking (adjacent) residues on either side of the selected residue) exhibit for the different conformational states. As indicated previously, these states are represented by the value r^2_θ of the lattice model. Since for every residue i there are seven distinct values of r^2_θ, corresponding to 18 distinct local conformational states, the local

energetic preference (denoted as parameter $\epsilon_\theta(r^2_{\theta i})$) for each of the states (r^2_θ values) must be specified. If it is desired to reduce the number of such adjustable parameters (that is, parameters requiring specification), the conformations (except conformations where $\epsilon_\theta\ (r^2_{\theta i})=0$) may be made isoenergetic and assigned the value $\epsilon_\theta > 0$.

In addition to bond angle, the torsional (dihedral angle) potential of a residue (i.e., its tendency to undergo an angle of rotation or twist) must be specified. The torsional potential associated with the i^{th} residue is specified in terms of residues (i-1) through (i+2). Actually, a dihedral angle potential must be specified in the model for all residues from residue 2 (corresponding to real residue 1) to residue n-2 (corresponding to real residue n-1). Because the model is confined to a lattice, it is convenient to describe the torsional potential associated with the i^{th} residue in terms of: (a) r^2_θ, $r^2_{\theta i+1}$, the bond angle states i and i+1, (b) r^2_ϕ, the square of the distance between α-carbons i-1 and i+2, and (c) the handedness of the dihedral angle, $\chi = +1$ for right-handed chirality (R) or $\chi = -1$ for left-handed chirality (L). For example, a planar state having $\phi = 0$ is specified by (16, 16, 37, -1). That is, the square of the distance between α-carbons i-1 and i+1 is 16, between α-carbons i and i+2 is 16, and between α-carbons i-1 and i+2 is 37. (For definiteness in the calculation, a dihedral angle of 0 is taken to be left-handed. This conformation could also be specified by the vectors b_i, b_{i+1}, b_{i+2} as shown in Figure 8). As many as 324 rotational states exist for each internal bond. These rotational states are all assigned a relative energy value $\epsilon_\phi\ (r^2_{\theta i}, r^2_{\theta i+1}, r^2_{\phi i}\chi)$. Generally, all

such rotational states are statistically weighted. Where the majority of the conformations are taken to be isoenergetic (with a small bias toward a small subset of conformations that are native), the short and intermediate range energetic preferences may be represented as $\epsilon(r^2_{\theta,i}, r^2_{\theta i+1}, r^2_{\phi i})$.

The seven lattice sites that define the α-carbon (Fig. 7) and the four lattice sites (Fig. 5) that define the surface 24 of the sidechain interact repulsively (i.e., with strong, hard core repulsion) with all the other α-carbons and their respective sidechains. In other words, no more than one sidechain or α-carbon can simultaneously occupy a given lattice site. (This is generally referred to as the excluded volume criterion.) Such a model may be viewed as having a backbone of finite thickness. In addition to the hard core repulsion, described above, there is a weak (soft core) repulsive interaction between non-bonded α-carbon backbone centers located within a distance of $\sqrt{5}$ model units of each other. If r_{kl} represents the distance between the k^{th} and l^{th} such centers, then the soft core repulsive energy ϵ_{rep} between the pair may be expressed as:

$$\epsilon_{rep} = \begin{bmatrix} \infty & ; & r^2_{kl} = 0,1,2,4 \\ \epsilon_{rep} & ; & r^2_{kl} = 3 \\ 3\epsilon_{rep} & ; & r^2_{kl} = 5 \\ 0 & ; & \text{otherwise} \end{bmatrix}$$

(ϵ_{rep} typically takes on the value of 6 in the calculations that follow.)

Following description of the lattice, bond angle, bond angle states, and torsional angles, a description of tertiary interactions between the residues in a three-dimensional setting is presented

next. To represent the effect of hydrogen bonding and dipolar-type interactions, a cooperative interaction energy parameter E_c is introduced which allows for secondary structure stabilization when any part of the α-carbon hard core envelope of the l^{th} residue is at a distance of 3 units from the α-carbon center of the k^{th} residue.

If a pseudodot product between two vectors is defined as:

$$\text{dot}(b_k, b_l) = \begin{bmatrix} 1 \ ; \ \text{if } b_k = \pm b_l \\ 0 \ ; \ \text{otherwise} \end{bmatrix}$$

then, the cooperative interaction energy ϵ_{ckl} may be given by:

$$\epsilon_{ckl} = \epsilon_c \left(\begin{matrix} \text{dot } (b_k, b_l) + \text{dot } (b_{k+1}, b_l) + \\ \text{dot } (b_k, b_{l+1}) + \text{dot } (b_{k+1}, b_{l+1}) \end{matrix} \right)$$

where, ϵ_c represents an energetic preference parameter which is applied, uniformly, to all residue pairs independent of their conformation.

Sidechain Interactions

In the preceding section, the subject of interactions relating to backbone conformation was discussed. In the following section, the subject of interactions between sidechains is discussed. Sidechain interactions are treated as being independent of backbone conformation. Interactions between any pair of side chains is allowed if the interacting sidechain sites lie at a distance of $\sqrt{2}$ from each other. Sidechains may be hydrophobic, hydrophilic or inert. Pairs of hydrophobic sidechains interact with an attractive potential of mean force; hydrophobic/hydrophilic pairs interact with a repulsive potential of mean force; and hydrophilic pairs interact weakly (i.e., weakly

attractive or repulsive with no change in quality to behavior).

With respect to the calculation of sidechain-sidechain interaction energy, the following rules (scales) were employed in one calculation: glycines were assumed to lack sidechains and were assigned a hydrophobicity index h(i) = 0. Hydrophobic residues were assigned a negative hydrophobicity index h(i) < 0, and hydrophilic residues were assigned a positive hydrophobicity index h(i) > 0. For all sidechains that were greater than two residues apart down the chain, the sidechain-sidechain interaction matrix am(i,j), representing the interaction energy between the i^{th} and the j^{th} pair of sidechains, was given in the form:

$$am(i,j) = -h(i) \cdot h(j) \cdot \epsilon$$

where $\epsilon = \epsilon_{phobe-phobe} > 0$, if h(i) and h(j) were both negative (that is, if both were hydrophobic). $\epsilon = \epsilon_{phobe-phil} > 0$ if one residue is hydrophobic and the other hydrophilic, and $\epsilon = -\epsilon_{phil-phil}$, (with $\epsilon_{phil-phil} > 0$), if both h(i) and h(j) are positive, that is, if both sidechains are hydrophilic. The subscripts phobe-phobe mentioned above represent interaction between two hydrophobic residues, phobe-phil represents interaction between a hydrophobic residue and a hydrophilic residue, and phil-phil represents interaction between two hydrophilic residues. (As indicated above and in the program listing shown in Appendix D, tertiary interactions between any spatially close pair of sidechains are implemented using a modified Miyazawa-Jernigan (MJ) hydrophobicity scale. Based on the frequency of occurrence of contacts between sidechain pairs in protein crystal structures, the MJ scale is used to

determine effective inter-residue contact energies.)

As used below, short-range interactions shall mean interactions between adjacent residues in the chain and does not include effects of their neighbors (i.e., neighboring residues in the chain). Medium-range interactions shall mean interactions between first, second, and third nearest-neighbor residue groups in the chain. Long-range interactions shall mean interactions between residues (not α-carbons) which are positioned greater than three nearest neighbors apart down the chain but which are spatially close (i.e., within 3°A of each other).

Both native and non-native interactions are allowed between non-bonded pairs of residues that are specially close enough to interact. No criterion or constraint is imposed to drive the simulation towards any predetermined native conformation. Based on long or short interactions, a native conformation may comprise one of a number of isoenergetic states. It is the juxtaposition of short-medium-and-long-range interactions, together with other factors described herein that produce the final result, namely a stable, folded conformation.

As described hereinafter, all of the energetic parameters, ϵ_{θ}, ϵ_{ϕ}, ϵ_{rep}, $\epsilon_{phobe\text{-}phobe}$, $\epsilon_{phobe\text{-}phil}$, $\epsilon_{phil\text{-}phil}$ are uniformly scaled by a reduced temperature factor, T.

With respect to specifying other characteristics of the primary sequence of amino acid residues, the following conventions are used. In a simplified model, the term $B_i(k)$ is used to represent the i^{th} stretch of k residues in the sequence. The k residues are represented as having identical ϵ_{θ} and $\epsilon\phi$ values and a marginal (short and intermediate range) preference for β-state conformation.

range) preference for β-state conformation. Consistent with β-sheet formation, $B_i(k)$ also represents an alternating odd/even pattern of hydrophilic and hydrophobic residues.

Where a sequence of k residues are locally indifferent to whether they are in an α-helix or in a β-sheet, the term $AB_i(k)$ may be used to denote the i^{th}-stretch in the amino acid sequence containing k residues in an alternating hydrophobic/hydrophilic pattern, such that $\epsilon_\theta(12) = \epsilon_\theta(16)$ for all k residues. Where a sequence of k residues has an alternating hydrophobic/hydrophilic pattern and locally prefers α-helical state conformation, such that $\epsilon_\theta(12) = 0$ and $\epsilon_\theta(16) > 0$, this is denoted by the shorthand notation $A_i(k)$.

Putative band regions are denoted by $b_i(j)$, and consist of j residues located at the interface between putative β-stretches i and i+1.

Chain Dynamics. Modification of Conformations

The dynamics of the chain are simulated by a (pseudo) random sequence of conformational rearrangements (moves) (i) through (iv) described below. In all such moves, the bead (amino acid residue) on which the move is performed is chosen at random.

(i) Examples of single bead jumps (also referred to as flips, spike or kink moves) are shown in Figure 9. Also, a representative set of single-bead modifications is listed in Table I. These moves are constructed by conserving the vector $b_{i-1} + b_i$ (i.e., not changing the magnitude nor direction of imaginary vector $(b_{i-1}+b_i)$). The moves are made in a manner which maintains the bond angle associated with the i^{th} residue but changes the bond angles of the i-

five distinct possible outcomes (associated with $r^2_{\theta i}$ = 12), each of the moves is coded with five outcomes, some of which are degenerate (i.e., their conformations, each has the same energy). A clock is used to sequentially choose the particular outcome. New conformations of jumps (kinks) are also generated at random. After a move has been selected, it is only accepted if the adjacent bond angles are allowed (i.e., $r^2_{\theta i+1}$, and $r^2_{\theta-1}$ must lie in the range 6-18). If the move satisfies these local geometric constraints, then the sites (seven backbone sites plus four sidechain sites) into which the bead will jump are checked to insure that they are unoccupied. Otherwise, the move is rejected (not made).

A list of sample single-bead, modified vector values is presented in Table I.

TABLE 1

Sample Single Bead Modification Data

CONFORMATION r^2_e	EXAMPLE SEQUENCE OF INITIAL VECTORS	POSSIBLE MODIFICATIONS
2 (excluded)	.....	.....
4 (excluded)	.....	.....
6	(2,-1,0) (0,2,1)	a. (0,2,1), (210) b. (2,0,-1), (0,1,2) c. (0,1,2), (2,0,-1)
8	(1,2,0), (-1,0,2)	a. (-1,0,2), (1,2,0) b. (1,0,2), (-1,2,0) c. (-1,2,0), (1,0,2)
10	(1,2,0) (2,-1,0)	a. (2,-1,0), (1,2,0)
12	(1,2,0), (1,0,2)	a. (1,0,2), (1,2,0) b. (2,1,0), (0,1,2) c. (0,1,2), (2,1,0) d. (2,0,1), (0,2,1) e. (0,2,1), (2,0,1)
14	(2,-1,0), (0,-2,1)	a. (0,-2,1), (2,1,0)
16	(1,2,0), (-1,2,0)	a. (-1,2,0), (1,2,0) b. (0,2,1), (0,2,-1) c. (0,2,-1), (0,2,1)
18	(-1,2,0), (0,2,1) or (-2,1,0), (-1,2,0)	a. (0,2,1), (-1,2,0) a. (-1,2,0),(-2,1,0)
20 (excluded)	.....	.....

(ii) With respect to two-bead end flips (in which the two end bonds are transformed to a new set of vectors), the set of two vectors is chosen at random from the twenty-four possible orientations of the lattice vectors. In this case, the two new end bond vectors must satisfy the allowed local bond angle criteria. If they do not, the move is be rejected. Further, the two end residues in their new conformation must not violate excluded volume constraints.

The above-mentioned moves (i) and (ii) satisfy the correct dynamics for the athermal random coil state in the absence of hydrodynamic interactions.

(iii) Turning now to chain rotations, an example of this type of move is shown in Fig. 10. The minimum size unit selected for rotation consists of three beads, and the maximum size unit is 2+wave. (The value of the parameter "wave" is generally 4, it is chosen so that the size of the unit undergoing the rotation is the size of a mean element of secondary structure.) The particular size of the unit (δ+1) undergoing the attempted rotation is chosen by the value of an external clock parameter, and sequentially varies from the minimum to maximum size. A particular bead I, at one end of the rotating unit, is chosen at random. For beads less than n/2, the unit undergoing the rotation is I-δ. For beads greater than n/2, the unit undergoing rotation is I+δ. If ib represents the first residue at the beginning of the rotating unit, and iend represents the residue at the end of the rotating unit, then if the bond angle state between the vectors b_{ib} and b_{iend-1} is a 14-18 state, the rotation is attempted. (The range of values of $r^2_{\theta i}$ is chosen so that the rotation

is physically possible.) The rotation is implemented by interchanging the two bond vectors (e.g., vectors 35, 37 joining randomly selected bead 39 shown in Fig. 10). The initial set of bond vectors joining residues ib to iend is (b_{ib}, b_{ib+1}, ... b_{iend-2}, b_{iend-1}). The final set of bond vectors is (b_{iend-1}, b_{ib+1}, ... b_{iend-2}, b_{ib}). The new conformation is checked to insure that it can join the remainder of the chain without violating bond angle restrictions and excluded volume restrictions.

(iv) Internal wave-like motions such as are shown in Figure 11 are also performed. These moves serve to propagate defects down the subchain by deleting a defect at one end of the subchain and creating the defect at the other end of the subchain. The defect propagation procedure is performed by the system as follows. I denotes a bead chosen at random. The system first determines if a U-shaped defect exists (i.e., does $b_I = -b_{I+3}$?). If not, attempt at wave-like motion is abandoned. If a defect exists, the system then picks a place where the defect should be inserted. The chosen point is at JJ = I+2 ± (5+δ), with δ varying between 0 and wave-1. About half of the time, the defect insertion point lies to the left of I, and the other half the time it lies to the right of it. As mentioned before, typically, the value 4 is selected for wave. As shown in Fig. 11, the bond vectors b_I 41 and b_{I+3} 43 are then sliced out of the chain, thereby deleting two beads 43 and 47, provided that b_{I+1} 49 and b_{I+2} 51, which will form the new bond angle state or vertex I+1 53, satisfy the local geometric constraints of the chain. Next, two bonds 49, 51 are inserted into the chain. If the original vectors associated with beads JJ-1 and JJ are b_{JJ-1} and b_{JJ}, the new set of

four vectors are (v, b_{JJ-1}, b_{JJ}, -v), where the vector v is chosen at random. Note that the intervening bond factors between I+4 and JJ-2 are left unchanged. A new conformation is then generated by renumbering the residues so that their identity is conserved. As before, both excluded volume and local bond angle criteria must be satisfied in order for the conformation to be accepted.

After each of the elemental moves (i) - (iv), described above, the energy of the new conformation, E_{nev}, is calculated and compared to the energy of the old conformation E_{old}. E_{nev} represents the sum of the individual energies, and is expressed as:

$$E_{nev} = E_\theta + E_\phi + E_c + E_s$$

where $E_\theta = \sum_{N} \epsilon_\theta$

$E_\phi = \Sigma_{tor}$

$E = \sum_{i,j} \epsilon_{ckl}$

and E_s (also referred to as E_{side}) $= 1/2_{i,j} \Sigma\ am(i,j)$

(The term E_{old} represents the initial total value, then successive previous total values with which E_{nev} is compared.)

With respect to free energy (as distinct from total energy), the system attempts to find a free energy minimum, given as:

Free energy = Total energy - TS

where T represents temperature, and S represents entropy.

If E_{nev} is less than E_{old}, then the conformation is accepted. Otherwise, a Metropolis

sampling criterion is applied (as described for example in *Monte Carlo Methods in Statistical Physics* 2nd ed. by K. Binder, Springer-Verlag, Berlin, New York, 1986). In which event, a random number R uniformly distributed between 0 and 1 is generated. If R is less than the probability P, where

$$P = \text{EXP}\ \frac{-(E_{new}-E_{old})}{K_B T}$$

then the conformation is accepted; otherwise, it is rejected. Here, k_B represents Boltzmann's constant and T represents the absolute temperature of the protein. Thus, a standard asymmetric Metropolis sampling scheme (criterion) is employed. As described below, the sampling scheme or criterion is applied in conjunction with a dynamic Monte Carlo technique (as described for example in *Monte Carlo Methods in Statistical Physics* by K. Binder, cited above).

A single Monte Carlo dynamics time step consists of N attempts at move type (i) (jump-type move) mentioned above, two attempts at move type (ii) where each of the chain ends are subjected to move type (ii), one attempt at move type (iii), and one attempt at move type (iv). In the simulation, the protein model is started out in a randomly generated high temperature (T) state. It is then cooled down, equilibrated, cooled further, until collapse to a folded conformation occurs. For each simulation run in the transition region between unfolded and folded states, at least 1.25×10^6 Monte Carlo time steps are sampled. The set of elemental moves employed in the simulation satisfies the well known stochastic kinetics master equation describing the dynamics of the system. (Refer, for example, to Appendix B.) In the limit (after a large number of steps), an

equilibrium distribution of states is generated.

With respect to the thermodynamics of folding, a detailed explanation is presented below. By restricting the protein to the lattice, it may be treated as a rotational isometric state model of the protein. First, the transition from the denatured to the native state is treated in the context of a two-state model. The free energies of the denatured state A_D, and the native state A_N are calculated as follows: A_D is calculated by neglecting all tertiary interactions in the denatured state (although pentane-like effects are included). In the calculation of A_D, long range excluded volume effects are neglected. For the calculation of A_N, small local fluctuations about the native state are neglected, and A_N is approximated by the energy of the native state E_N.

In the context of a two-state model for folding, the fraction of molecules in the native state, f_N, is given by

$$f_N = \frac{\exp(-(E_N - A_D))}{[1+\exp(-(E_N - A_D))]}. \quad (2)$$

where A_D is given as:

$$A_D = K_B T \ln(Z_D) \quad (3)$$

(The term Z_D may be expressed as $Z_D = J \prod^{N-1} V_{D,i} J$, as defined in Appendix C.)

In the context of the two-state model, the mean square radius of gyration $\langle S^2 \rangle$, defined as

$$\langle S^2 \rangle = \frac{\sum_{i=1}^{N} (r_i - r_{cm})^2}{N} \quad (4)$$

with $|r_i-r_{cm}|$ representing the distance of the i^{th} bead from the center mass r_{cm}, may be expressed as

$$<S^2> = f_N<S_N^2>+(1-f_N)<S_D^2> \quad (5)$$

where $<S_N^2>$ and $<S_D^2>$ are the mean square radii of gyration in the native and denatured state, respectively.

The above explanation may be used to select appropriate temperature values for use in the simulation. Substantial computer time can be saved by avoiding high temperatures associated with the denatured state. Also, temperatures that are too low can drastically quench the system.

Conformational Transitions

As shown below, conformational transitions can be approximated by a two-state model, or can be determined directly from folding trajectories.

In the following paragraphs, the requirements for folding to a unique conformation (e.g., a four-member β-barrel state) are described. Figs. 12A-D show a segment with backbone α-carbons **101** and interacting sidechain sites **103**. Also shown in the top view are hydrophobic core **105** with the interdigitating sidechains **107, 109**. Also shown are the corresponding conformations **111, 113** with α-carbons alone.

The first of the three native turns is shown to involve the eight through eleventh residues with backbone bond angle conformations 18, 8, 18, and 10, respectively. The central turn is shown to involve a crossover connection between the two anti-parallel β-strands, and involves the eighteenth through twentieth residues with backbone bond angle conformations 14, 10, and 18. The remaining outer

turn is shown to involve residues the twenty-sixth through twenty-ninth residues in bond angle conformations 12, 14, 14 and 8. The remainder of the bond angle states are all 16-type states. Thus, a planar β-sheet is assumed. Within an anti-parallel β-hairpin, the α-carbons are shifted with respect to each other by one lattice unit. This allows for the interdigitation of the side chains mentioned above. In the fully native conformation, there are twenty contacts between neighboring sidechains (i.e., twenty pairs of sidechain interacting sites that are a distance of $\sqrt{2}$ from each other).

In the conformation considered here, the pattern of hydrophobic and hydrophilic residues is the same. The model chain consists of N=37 residues. In each of the strands, all of the even (odd) residues are hydrophobic (hydrophilic). The first strand consists of the first through eighth residue. The ninth through eleventh turn residues are all hydrophilic. The second strand runs from the twelfth to the eighteenth residue, with all the even (odd) residues hydrophobic (hydrophilic). The nineteenth and twentieth turn residues are, respectively, hydrophilic and hydrophobic. The third strand runs from the twenty-first to the twenty-sixth residue. The twenty-seventh through twenty-ninth are turn residues, all of which are hydrophilic. The fourth strand runs from the thirtieth to the thirty-seventh residue. The first and last residues (one and thirty-seven) are virtual residues (i.e., they are devoid of sidechains, but they do occupy excluded volume). They may be regarded as capping the two ends, and are included so that the bond angle state for the real residues (the second and thirty-sixth residue) may be defined.

Turning now to the subject of equilibrium folding, the requirements for equilibrium folding of a region of the chain to its unique, native structure (e.g., the four-member β-barrel structure) is described. The interplay of an intrinsic native turn propensity and a short- and medium-range preference for β-sheet formation is described.

In one simulation operation, for the sequence $B_1(7)b_1(4)B_2(6)b_2(3)B_3(5)b_3(4)B_4(8)$ the parameter $\epsilon_\theta(16)$ was found equal to zero for the B_i state and -0.25/T for all the other states. For the B_i state the parameter $\epsilon_\phi(16,16,37) = .6/T$, and is zero for all other states. For the turns b_i: $\epsilon_\theta=0$ for the native conformation, and $\epsilon_\theta=.25/T$ for all other conformations. Similarly, $\epsilon_\phi = .6(1.75)/T = -1.05/T$. $\epsilon_{phil\text{-}phil} = .25/T$, $\epsilon_{phil\text{-}phob} = 1./T$, and $\epsilon_{phob\text{-}phob} = -.75/T$. The cooperativity parameter $\epsilon_c = -.15/T$. In the native conformation, the total short range free energy $E_\theta = 0$, the total torsional energy $E_{tor} = -25.8/T$, the total sidechain interaction free energy arising from hydrophobic interactions $E_{side} = -14.25/T$, and the cooperative interaction free energy $E_c = -11.25/T$. Thus, the total energy of the native state $E_N = -51.3/T$. A summary of the conformational properties of this sequence, as well as all the other types of primary sequences, is presented in Table II. The primary sequence is designated by a shorthand notation $\epsilon_\alpha > \epsilon_\beta, 1., 1.75$. This notation indicates that, based on bond angle preferences, β-conformations are locally preferred for the B_i portions of the primary sequence, and that the torsional angle preference ϵ_ϕ (for native-like conformations in the B_i region) is locally favored by a ratio of 1:1.75 over that in the turn region.

TABLE II
Compilation of Selected Folding Results

Sequence	No. of Folding Attempts	No. of Successful Folds	Intrinsic Turn Probability
$\epsilon_\alpha > \epsilon_\beta$; 1. 1.75	5	5	0.0046
$\epsilon_\alpha > \epsilon_\beta$; 1.; 1.5	6	4	0.0021
$\epsilon_\alpha = \epsilon_\beta$; 1.; 1.5	6	6	0.0025
$\epsilon\alpha = \epsilon_\beta$; 0.5; 1.5	7	5	0.0093
$\epsilon_\alpha = \epsilon_\beta$; 0.; 1.5	11	5	0.063
$\epsilon_\alpha = \epsilon_\beta$; 0.; 1.75	10	10	0.14
$\epsilon_\alpha < \epsilon_\beta$; 1.6; 0.05.	11	11	0.036
$\epsilon\alpha = \epsilon_\beta$; 1.; 0	14	0	5×10^{-5}

In the absence of long-range interactions, there is a negligible intrinsic preference for the native conformation. To address this point, reference is made to equations 2-5. Using equations 2-5, the transition midpoint (including tertiary interactions) is predicted to be near T = 0.576. Employing equation (3), it is found that at this temperature $A_D = -88.44$, and that E_N (without tertiary interactions) equals -44.79. The fraction of molecules in the native conformation which would be present if all tertiary interactions are turned off (that is, the equilibrium population based on short and medium range interactions embodied in E_θ and E_{tor} alone) is given by

$$f^\circ_N = \exp(-E_{tor}) \; / \; \exp(-A_D). \qquad (6)$$

Using equation 6, f°_N is found to have the value:

$f^\circ_N = 1.11 \times 10^{-19}$.

Thus, there appears to be a negligible

preference for the native state in the absence of long range interactions, suggesting that finding of the native conformation is by no means guaranteed by the above choice of short and medium range interaction parameters. Rather, this chain will thrash about until it finds the native state.

The next subject described below is the nature of the conformational transition itself. In Figs. 13A-C, the average number of native contact pairs between sidechains (N_c) versus time, is plotted for a chain under denaturing conditions at T = 0.6, in the thermal transition region at T = 0.58, and under strongly renaturing conditions at T = 0.545. The times indicated in the figure are in units of 500 Monte Carlo steps, and the fully native molecule contains twenty contact pairs. Under denaturing conditions, N_c fluctuates around zero, characteristic of a relatively short, unfolded chain. In the transition region, the system starts out unfolded, and then around t/5000 = 118, it undergoes a rapid transition in about 6,500 Monte Carlo time steps to the fully native molecule. For the remainder of the time, it stays in the native state. Other conformational properties (not shown), such as the energy, the instantaneous value of the radius of gyration, the total number of contact pairs $N_{c,tot}$ also undergo sharp changes in value that is a characteristic of an all-or none transition (i.e., a transition where the intermediates between the denatured and fully folded states are marginally populated). On further cooling to T = 0.545, the chain becomes fully native, with minor oscillations in N_c arising from the fluctuations of the ends residues of the chain.

Decreasing the turn propensity for native-

like states decreases the stability of the native conformation and decreases the transition temperature. In the transition region, however, not only are native in-register four member β-barrels observed, but so are out-of-register conformations in which one of the exterior strands is two residues out-of-register, shifting the native contact between sidechains two and thirty-six to a non-native contact of residues two through thirty-four in one case, and to a non-native sidechain contact of residues four through thirty-six in the other case. In the former case, the outer turn began at residue twenty-five instead of residue twenty-six, thus, pushing the outer strand beyond the end of the barrel; and in the latter case, the turn began at residue twenty-eight and involved five residues, producing a bulge. Out of a total of six conformational transitions to a folded state, four folded directly to the native conformation, and two produced the out-of-register states described above.

The out-of-register state associated with residues four through thirty six occurred at relatively high temperature and folded in about 65,000 Monte Carlo steps. It remained folded for 315,000 time units before unfolding in about 165,000 time units.

Many out-of-register conformations have the same number of contacts between hydrophobic sidechains as in the native state; they differ in the cooperative free energy between the strands and in the local conformational preferences. Dropping the turn preference, increases the population of these out-of-register states. It is seen, therefore, that in the absence of some intrinsic preference for secondary structure, many in-register and out-of-

register conformations can be generated, and it is the marginal intrinsic turn propensities which act to select from among them one conformation as the unique folded form. Based on tertiary interactions between hydrophobic sidechains alone, many otherwise degenerate conformations can be generated. Here, a marginal preference for β-strand secondary structure plus the presence of turn neutral regions are required for folding to occur to a unique native state. Here, turn propensities of 1% or lower (see below, and Table II) are sufficient to yield folding to the native barrel of Figure 12.

It has been found that as the local propensity for β-states decreases, there is an increasing population of non-native turns and out-of-register states, even though the native turn population increases as T decreases. To fold the system to the global free energy minimum that corresponds to the native conformation, therefore, the free energy of out-of-register conformations should be increased relative to in-register conformations. As the local preference for β-states decreases, it becomes easier to form non-native turns; this appears to be the origin of the out-of-register states. Therefore, since the number of contacts between sidechains is approximately the same for the in-register and out-of-register cases, what determines the native conformation is the number of cooperative-type interactions, ϵ_c, plus the differences in local conformational preferences. Where the local preference difference is decreased, a number of out-of-register states that are in deep local minima is observed.

For a primary sequence of the type $\epsilon_\alpha = \epsilon_\beta$; 0, 1.5 (which is similar to the above cases, except

that the torsional potential in the putative β-strand is disregarded), the β- and α-states are locally isoenergetic. The particular sequence of the AB_1 stretches are induced by tertiary interactions. In all cases, the folded conformations turn out to be β-barrels. Thus, tertiary interactions taken with local turn propensities provide for selection of β-collapsed states. Where the transition temperature is reduced, the native turn populations become greater. For example, the calculated turn population of native turn one is about 10% at T = 0.40. Based on tertiary interactions alone, the unique native state is not achieved. This is most likely due to the degeneracy in sidechain contacts between the in-register and the two residue out-of-register conformers. If native turn propensity is sufficiently augmented, it appears that tertiary interactions plus intrinsic turn propensities are sufficient to yield the unique native state. Further, if the short-range interactions favoring β-strand formation are decreased, turn formation at a non-native location becomes more likely and, thus, the intrinsic turn propensity must be augmented (see Table II) to insure the recovery of a unique conformational state.

Next examined were sequences of the type $A_1(7)b_1(4)A(6)b_2(3)A_3(5)b_3(4)A_4(8)$; that is, molecules having the sequence $\epsilon_\alpha < \epsilon_\beta$; 0, 1.6; 0.05, where the nature of the conformational transition for model proteins whose β-strands in the denatured state locally favor α-helix conformation, but whose amino acid pattern still consists of alternating hydrophobic and hydrophilic residues. For A_1, it has been found that $\epsilon_\theta(12) = 0$, $\epsilon_\theta(16) = 0.05/T$, and for all the others $\epsilon_\theta = .25/T$. Furthermore, it was found

that $\epsilon_\phi = 0$ for all the residues in A_1. These systems (where the local preference is for an α-helix conformation but the global free energy minimum conformation is that of a β-strand) spend substantial time trapped in relatively deep local minima. As the local preference for helical conformations is increased in the putative β-strand forming regions, while the unique four-member β-barrel is sometimes obtained, the chain generally thrashes about for over many millions of time steps (e.g., over 50 million) without finding a unique folded form.

An important indication from these simulation results is that a marginal local turn preference plus tertiary interactions are sufficient to produce unique native conformations, even in the extreme situation where the local conformational preference is for helices rather than β-sheet. If the native conformation is in thermodynamic equilibrium, then it is deemed to be at the lowest free energy state (conformation), independent of how the free energy is divided. That is, while it is conceptually convenient to divide the free energy into short-, medium- and long-range interaction contributions, it is the sum of these contributions, i.e., the total free energy, that determines the equilibrium conformation. The approach taken by the simulations show that the local minima problem can be surmounted to recover the lowest free energy structure, which overrides local considerations if there is a marginal turn propensity for native-like turns. Thus, turns appear to play an extremely important role in determining the ability to recover a unique native conformation.

Folding Pathway (Trajectory)

Turning now to a discussion of the folding pathway, it is seen that the sequence defines an observable pathway (trajectory) as it folds and makes the transition from its denatured (unfolded) conformation state to its native (folded) conformation state. A trajectory of a sample having the primary sequence $\epsilon_\alpha > \epsilon_\beta$, 1., 1.75, is shown in Figs. 14A-B. The conformations at different times, are shown at different orientations that aid in the visualization of the folding process. At t = 585,800 Monte Carlo time units, folding is seen to initiate from the central turn **115** between the β-hairpin composed of strands two **117** and three **119**. (Folding is not unidirectional. β-strands may dissolve, as well as form, during the course of assembly.) If the conformation at t = 585,900 is compared with that at t = 586,000, it will be seen that a slight dissolution of the β-hairpin **121** has occurred. By t = 586,300, the first β-hairpin **121** is almost fully assembled. However, by t = 586,550, the majority of one of the two strands in the β-hairpin dissolves and, then, reforms at t = 586,600. Then, there is a pause as the random coil tail **123** thrashes about, until the next native-like turn **125** forms. By t - 587,700, three of the four β-strands **117**, **119**, **127** are essentially in place. Thus, assembly to the three-member β-barrel intermediates takes 1,900 time steps from the beginning of folding. Throughout this process, the excluded volume of the chain hinders assembly. Most of the configurations of the denatured tail are nonproductive; the tail thrashes about until t = 591,800 when it works its way into a position(s) that permits native state assembly. After which, the assembly becomes more rapid and, by

t = 592,250, the fully folded molecule forms. Thus, the three-member β-barrel is the long-lived intermediate, living for 4,550 time steps or 71% of the total elapsed time from the start of folding. The mechanism of assembly is best described as punctuated, on-site construction.

With respect to unfolding of a tertiary structure, in all instances unfolding is the reverse of folding. Typically, unfolding starts with either one of the external strands becoming denatured or an internal stand closest to the denatured tail becoming unfolded.

Computer System and Method

Referring now to Figs. 3 and 15, a system and method are shown and described for simulating protein folding and determining three-dimensional (tertiary) structures of proteins.

The system comprises an input means **57** such as a keyboard for specifying (entering) selected amino acid sequences and other data such as temperature and fold preferences, a RAM (random access memory) **59** for storing such data, a ROM (read-only memory) **61** with a stored program, a CRT (cathode ray tube) display unit **63** and/or printer **65**, an optional auxiliary disk storage device **67** for storage of relevant data bases, and a microprocessor **69** for performing, under control of the stored program, the steps of processing the entered data, simulating the folding of the protein from its unfolded state to its folded (tertiary) state, and displaying via the display unit (or printer) tertiary conformations of the protein in three dimensions.

A user enters the amino acid sequence data

file from the auxiliary storage unit). In response to entry of the sequence data, the system inputs (specifies) the data for processing, stores the data in memory then processes it as shown in Figs. 15A-F. Sample data of the type which may be input to the system is shown in Appendix E. In processing the data, the system generates a tertiary interaction matrix as shown in Appendix E and produces, in addition to a display of the protein's tertiary structure, a sample output as shown in Appendix E for tracking the simulation. As indicated above, the system operates under the control of a stored program. A listing of the program is shown in Appendix D.

Turning now to Figs. 15A-F, in response to the specified data the system generates a random conformation of backbone and sidechain elements (residues). It does this by generating a set of random bond angles, then generating the coordinates of the backbone and sidechains as a starting chain in a 210 lattice (Fig. 4). The system then checks to determine if the excluded volume criterion is met, after which, it constructs an interaction table, a sample of which is shown in Appendix E. It proceeds to construct the interaction table by first establishing respective bond angle preferences, then establishing dihedral (rotational) angle preferences followed by establishing side-chain interaction criteria. The system then stores the temperature, bond angle, lattice coordinates, preferences, and interaction data in a table or matrix like that shown in Appendix E. Thereafter, the system reads the data from the table and constructs, by means of Monte Carlo simulation, a random conformation; following which, the system calculates the total energy of the

conformation represented as (E_{old}). Thereafter, the system selects (at random by Monte Carlo simulation) a pair of bond vectors for rotation. It then checks if the rotation would violate the excluded volume criterion. If it would, the rotation is not attempted, and the system proceeds to the next step. If it would not violate the excluded volume criterion, another check is made to determine if the bond angles subtended by the bond vectors are between 14 and 18; if they are, it attempts the rotation. Otherwise, it does not attempt the rotation and proceeds to the next step. In performing rotation, the system modifies the conformation by interchanging a randomly selected pair of bond vectors. In other words, it proceeds to change the rotation angle ϕ. Thereafter, the system proceeds to determine the coordinates of lowest energy conformation which satisfy the Metropolis criterion. It does this by first calculating the total energy (E_{new}) of the new modified conformation then comparing the total energy E_{new} with the total energy of the old conformation E_{old}. If E_{old} is greater than E_{new}, then the coordinates of the old conformation are replaced with the coordinates of the new conformation. The system then proceeds to the next step (step B) which is be described below. If E_{old} is not greater than E_{new} then, in compliance with the Metropolis criterion, a random number R is generated and the probability

$$P = e^{\frac{-(E_{new}-E_{old})}{K_B T}}$$

is calculated. That probability is compared with the random number R. If R is less than P, the coordinates of the old conformation is replaced with the coordinates of the new conformation and the system proceeds to the next step (step B). If,

however, R is not less than P, the system directly proceeds to the next step (Step B). At the next step, the system proceeds to choose a bead at random to move within the lattice. Before moving the bead, the system tests if the move (which is a jump-type move) would violate the excluded volume criterion. If no, it proceeds with the move. If yes, it does not proceed with the move, and proceeds instead to choose the next bead until all the beads in the chain have been checked for modification (movement). If the move would not violate the excluded volume criterion, the conformation is modified by moving the bead to a new lattice site. In other words, the bead would make a jump move which would change its coordinates and associated bond angle θ. After the move is made and the conformation is modified thereby, the system calculates the total energy of the new conformation, that is, the total energy E_{new} in a similar manner as indicated earlier. E_{new} is then compared with E_{old}, the energy of the previous conformation before the move. If E_{old} is greater than E_{new}, then the coordinates of the old conformation are replaced with the coordinates of the new, and the next bead move is checked. If E_{old} is greater than E_{new}, then the Metropolis criterion is applied (and the random number R is generated, and the probability P is calculated in the same manner as indicated earlier, as shown in Fig. 15A-F), and the random number R is compared with the probability P. If R is less than P, the coordinates of the old conformation are replaced with the coordinates of the new and the next bead move is checked. If R is not less than P, the next bead move is checked and the loop is repeated until all bead moves (i.e., the moves of all n beads) have been checked, at which time if all bead

moves have been checked the system proceeds to the next step (step C). At this next step, the system proceeds to process the two end beads. It identifies the first end bead then checks if an end flip-type move would violate the excluded volume criterion. If no, it proceeds with the move. Otherwise, it aborts the move and proceeds to check the second end bead. In the event the move of the first end bead would not violate the excluded volume criterion, the system proceeds to modify the conformation by performing an end-flip move that changes the coordinates of the end bead. It then proceeds to determine the coordinates of the lowest energy conformation which satisfies the Metropolis criterion in the same manner as it did for the rotational and jump-type moves. After determining the coordinates of the lowest energy conformation which satisfy the Metropolis criterion, the system checks if both end beads are processed. If the second end beads remain to be processed, the system identifies the second end bead and proceeds to check whether an end flip move of the second end bead would violate the excluded volume criterion. If it would violate the criterion and both end beads have been considered, it then proceeds to the next step (step D). If it does not violate the criterion, then the system proceeds to modify the conformation by performing an end-flip move of the second end bead changing the coordinates of the second end bead. It then proceeds to determine the coordinates of the lowest energy conformation which satisfy the Metropolis criterion, after which it proceeds to the next step (step D). At this next step, the system selects a bond at random then searches for a U-shaped segment. It then checks, after finding the U-shaped segment, whether a move of a translation (wave

motion) type move would violate the excluded volume criterion. If not, it proceeds with the modification. If it does violate the excluded volume criterion, it aborts the move and proceeds to check if all the jump-type moves were made. If all were made, it proceeds to the next step (step E). However, if the move would not violate the excluded volume criterion, the system proceeds to modify the conformation by performing the translation/wave-motion-type move changing the coordinates of the beads defining the U-shaped segment. The system then determines the coordinates of lowest energy conformation which satisfy the Metropolis criterion, after which it proceeds to check if all the jump-type moves were made. If all the jump-type moves are not made (completed), it starts the loop again. One complete loop is represented by one rotational move, n jump-type moves, two end-flip moves, and one U-shaped move. After the loops have been completed and all moves made and/or aborted, the system checks to determine if the chain is still positioned near the center of the lattice. If it isn't, it moves the chain to the center of the lattice and adjusts its coordinates accordingly. Thereafter, the system displays a three-dimensional representation of the protein structure and repeats the process (processing) for a predetermined number of times. However, if upon checking whether the chain is still positioned near the center of the lattice, it finds that it remained at the position near the center of the lattice, the system immediately proceeds to displaying the three-dimensional representation of the protein, then repeats the process. After the three-dimensional coordinates of the tertiary protein structure are generated for display, a graphics

program such as SYBYL (which is commercially available from Tripost Associates Corporation of St. Louis, Missouri) is used by the system to display the tertiary structure corresponding to the coordinates. Sample display output is presented in Fig. 1. Sample printed output is presented in Appendix E.

An alternative embodiment of the system is presented in Fig. 16 comprising a keyboard **151** for entering data representing temperature and amino acid sequences, a RAM **153** for storing the entered data, and a unit **155** for generating a representation of a lattice, including unit **157** for positioning lattice sites, and unit **159** for positioning α-carbons relative to the lattice sites. The system includes a unit **161** for combining the generated lattice representation and the sequence of residues, a unit **163** for producing representations of protein structures, and a unit **165** for comparing the protein structure representations to a predetermined criterion and for selecting one of the protein structure representations for display.

APPENDIX A

The following is a description of various lattice model rules which must be followed for constructing conformations of various sidechains linked to various backbone configurations.

As shown in Figure 8, let the i^{th} bond vector b_i connect α-carbons (i-1) and (i). Then, for a given backbone conformation, r^2_θ may be defined as follows:

$$r^2_\theta = (b_i+b_{i+1})^2$$

On the 210 lattice, the allowed values of r^2_θ are 6,8,10,12,14,16 and 18. Any other value of r^2_θ is rejected as not realistic or not representable on the 210 lattice. For a given backbone conformation, four sidechain vectors are constructed. The center of sidechain interaction is located at the site defined by a diamond lattice vector d 34, of the type (±1,±1,±1), which points from the center of the α-carbon to the point (±1,±1,±1). The other three vectors f_1, f_2 and $f_{3\ 36,38,40}$ are of the fcc type, whose sum is twice that of the diamond lattice vector d 34. The vector d has left-handed chirality (L). With respect to the backbone, vector d points toward the N-terminus of the sequence. The orientation angle is generally not less than 60°.

Pseudovector p is defined as the cross-product of b_{i+1} and b_i:

$$p = b_{i+1} \otimes b_i$$

and w is defined as:

$$w = b_i - b_{i+1}$$

Appendix A (Cont'd)

The general procedure for the calculation d, f_1, f_2 and f_3 is given as follows: If $d = (d_x, d_y, d_z)$, then

$$f_1 = (d_x, d_y, 0)$$
$$f_2 = (d_x, 0, d_z)$$
$$f_3 = (0, d_y, d_z).$$

In the following, use is made of the function isgn(x), where:

$$\text{isgn}(x) = \begin{cases} 1 & x \geq 0 \\ -1 & x < 0 \end{cases}.$$

If $r^2_\theta = 14$, then

$$d_x = \text{isgn}(p_x)$$
$$d_y = \text{isgn}(p_y)$$
$$d_z = \text{isgn}(p_z)$$

If $r^2_\theta = 8, 12$ or 16, then

$$d_x = \text{isgn}(p_x - 2b_{x,i+1})$$
$$d_y = \text{isgn}(p_y - 2b_{y,i+1})$$
$$d_z = \text{isgn}(p_z - 2b_{z,i+1})$$

where

$$b_{i+1} = (b_{x,i+1}, b_{y,i+1}, b_{z,i+1}).$$

If $r^2_\theta = 6$ or 10, then

$$d_x = \text{isgn}(p_x + w_x)$$
$$d_y = \text{isgn}(p_y + w_y)$$
$$d_z = \text{isgn}(p_z + w_z)$$

Appendix A (Cont'd)

And, if $r^2_\theta = 18$, and if $p_x \cdot p_y \neq 0$, then

$$d_x = \text{isgn}(p_x)$$
$$d_y = \text{isgn}(p_y)$$
$$d_z = \text{isgn}(p_z).$$

Otherwise,

$$d_x = \text{isgn}(p_x+w_x)$$
$$d_y = \text{isgn}(p_y+w_y)$$
$$d_z = \text{isgn}(p_z+w_z).$$

APPENDIX B

A generalized master equation is shown below:

$$\frac{\partial p(\{i\},t)}{\partial t} = \sum_{\{i'\}} \ldots \Sigma\, k_f p(\{i\}|\{i'\}) q(\{r_{i'}\}) - k_b p(\{i'\}|\{i\}) q(r_{i'}) \quad (1)$$

where

$\{i\}$ represents a first set of vectors;

$\{i'\}$ represents a second set of vectors;

$p(\{i\},t)$ represents the probability of finding a set of vectors $\{i\}$ at a time t;

k_f represents rate of increase of the set $\{i\}$ in size (membership) due to move of bead from set $\{i'\}$ to set $\{i\}$;

k_b represents rate of decrease of the set $\{i\}$ in size due to move of bead to set $\{i'\}$ from set $\{i\}$;

$\{r_i\}$ and $\{r'_i\}$ represent coordinates of the set of bond vectors $\{i\}$ and $\{i'\}$;

$q(\{r_i\}_{\{i'\}})$ represents an excluded volume function

= 1; if $(r_{i'})$ are unoccupied

0; if $(r_{i'})$ are occupied

$p(\{i\}|\{i'\})$ represents the probability of occupying set $\{i\}$ upon moving from set $\{i'\}$;

$p(\{i'\}|\{i\})$ represents the probability of occupying set $\{i'\}$ upon moving from set $\{i\}$;

and the relationship between k_f and k_b may be expressed as:

$$\frac{k_f}{k_B} = \exp\left(-\frac{(U\{i\}-U\{i'\})/}{k_B T}\right.$$

Appendix B (Cont'd)

where U(i) represents the total energy of the protein in the i^{th} conformation;

U(i') represents the total energy of the protein in the i'^{th} conformation;

k_B represents Boltzmann's constant; and

T represents temperature (in degree Kelvin) of the protein.

A bead represents an amino acid residue comprising a full sidechain (i.e., four lattice sites) and backbone segment (i.e., seven lattice sites). A bead is shown, for example, in Figures 5 and 9. In terms of the above equation, the probability of finding a set of vectors (i,i+1) at a time t in a two-bond jump-type move of a bead from one coordinate position (r_i) to another coordinate ($r_{i'}$) may be expressed as:

$$\frac{P((i,i+1),t)}{t} = \sum_{\substack{i',i'+1 \\ \theta_{i',i'+1}=\theta_{i,i+1}}} k_f\, P(i;i+1|i';i'+1;\theta)q(r_i) - k_b\, P(i';i'+1|i;i+1;\theta)q(r_{i'})$$

where,

i and i+1 represents a first pair of vectors;

i' and i'+1 represents a second pair of vectors; and

θ represents the bond angle between vectors (bonds) i and i+1 and between i' and i'+1.

In addition to the single-bead jump-type move described above, a conformation may be modified by rotational and/or translational motion of one or more beads, as shown for example in Figures 10 and 11.

Appendix C

Calculation of the Denatured State Free Energy

In this appendix, an expression for the free energy of the unfolded state of a model protein confined to a 210 lattice is calculated. Two cases are examined. The first corresponds to the situation when the torsional potential ϵ_ϕ equals zero, and the second corresponds to the more general case when ϵ_ϕ is non-zero.

With respect to the lattice, each of the twenty-four possible vectors connecting the lattice sites may be given a number one through twenty-four, as follows:

1=(2,1,0)	13=(0,-1,-2)	
2=(2,0,1)	14=(0,-2,-1)	
3=(2,-1,0)	15=(0,1,-2)	
4=(2,0,-1)	16=(0,-2,1)	
5=(1,2,0)	17=(-1,2,0)	
6=(1,0,2)	18=(-1,0,2)	
7-(1,-2,0)	19=(-1,-2,0)	(C-1)
8=(1,0,-2)	20=(-1,0,-2)	
9=(0,1,2)	21=(-2,1,0)	
10=(0,2,1)	22=(-2,0,1)	
11=(0,-1,2)	23=(-2,-1,0)	
12=(0,2,-1)	24=(-2,0,-1).	

To specify the conformation of the chain, given the location of the first bead, a sequence of N-1 numbers, ranging from 1 to 24, is specified with the first bond vector (vector 1) chosen arbitrarily as vector (2,1,0), the second vector must satisfy the constraint $6 \leq r^2_\theta \leq 18$. There are 18 such possibilities, and there are four states such that $r^2_\theta = 6$. The second vector can be (0,-2,±1) and (-1,0,±2). There are two such possibilities when $r^2_\theta = 8$, namely (0,-1,±2). When $r^2_\theta = 10$, there are two possibilities as well, (-1,2,0) and (1,-2,0). If $r^2_\theta = 12$, again, there are two possibilities with the allowed second vectors being (0,1,±2). Turning to the $r^2_\theta = 14$ case, there are a total of four possibilities (0,2,±1) and (1,0,±2). If $r^2_\theta = 16$, there is one

possibility, (2,-1,0). Finally, for r^2_θ =18, there are three possibilities (2,0,±1) and (1,2,0). In general, for a given vector number i, there are eighteen allowed vectors; subsequent allowed vectors vary depending on the particular vector that precedes them.

A pseudo inner product may be defined (by analogy to orthonormal basis sets) as follows:

$$\langle i,j\rangle = 1, \tag{C-2}$$

if the two vectors i and j are allowed, and

$$\langle i,j\rangle = 0, \tag{C-3}$$

if the two vectors i and j are not allowed.

Denatured state partition function ϵ_ϕ =0

In the absence of a torsional potential that serves to couple adjacent bond angle states (and which, therefore, introduces cooperativity into the model), the internal partition function of the denatured state, Z^0_D, may be obtained from

$$Z^0_D = J^* \prod_{i=2}^{N-1} U_{D,i} J, \tag{C-4}$$

where J is a row vector of dimension 24, consisting of a 1 followed by twenty-three zeros, J is a column vector consisting of twenty-four ones, and $U_{D,i}$ is a 24 x 24 matrix associated with the ith residue, each row of which contains 18 non-zero elements and 6 zero elements. $U_{D,i}$ may be expressed as:

$$U_{Di}(k,l) = \langle k,l\rangle \exp(-\varepsilon_{\theta,i}(k,l)/k_B T). \tag{C-5}$$

As shown below, the configurational partition function can be written as the product of the internal bond angle partition functions associated with each bond angle state $Z_{\theta,i}$:

$$Z_D^0 = \prod_{i=2}^{N-1} z_{\theta,i} \qquad (C-6)$$

The matrix product in equation C-4 is of the form:

$$Z_D^0 = \sum_{k=1}^{2\ell}\sum_{l=1}^{2\ell}\cdots\sum_{r=1}^{2\ell}\sum_{s=1}^{2\ell} U_{D,2}(1,k)U_{D,3}(k,l)\cdots U_{D,N-2}(u,r)U_{D,N-1}(r,s) \qquad (C-7)$$

Given that the sum of all the elements in the columns is independent of the row index (i.e., each row has the same set of bond angle states that must be summed over), the sum of the products can be expressed as the product of the sums, as follows:

$$Z_D^0 = \prod_{i=2}^{N-1}\sum_{k=1}^{2\ell} U_{D,i}(1,k) \qquad (C-8)$$

which is identical to equation C-6 because $z_{\theta,i}$ is the same as

$$z_{\theta,i} = \sum_{k=1}^{2\ell} U_{Di}(1,k) \qquad (C-9)$$

Thus, the separability of the partition function is established. The free energy of the denatured state is simply

$\underline{\epsilon_\phi \neq 0}$

$$A_D^0 = -k_B T \ln(Z_D^0) \qquad (C-10)$$

To include the effect of non-zero ϵ_ϕ into the calculation of the partition function, the chain is divided into statistical weight matrices associated with pairs of bonds. That is, the partition function is calculated as

$$Z_D = J_{576} \prod_{i=2:\text{even } i}^{l_u} U_i^{\phi} J_{576} \qquad (C-11)$$

where J^*_{576} is a row vector of dimensionality 576 whose first term is unity and remaining terms are zero. J_{576} is a column vector of dimensionality 576, all of whose elements are unity. $l_u = N$ if N is even, and $l_u = N-1$ if N is odd. U^{ϕ}_i is a 576 by 576 matrix. For convenience in setting up U^{ϕ}_i, the torsional angles are labeled from 3 to N-1, rather than from 2 to N-2 as in the main text. For i=2, one merely has to account for the bond angle

associated with the second residue. Choosing the first bond as vector 1, the only non-zero elements of U^{ϕ}_2 are

$$U^{\phi}_2(1,j) = \langle 1,j \rangle \exp(-\varepsilon_{\phi,2}(1,j)/k_B T). \quad \text{(C-12)}$$

We next consider the case where $2<i<l_u$. Let the bond vectors associated with residues i-3, i-2, i-1 and i be labelled by j,k,l,m, respectively. The jth bond vector connects residues i-3 to i-2. The rows of U^{ϕ}_i (row,column) are obtained from j and k by

$$row = (j-1)24 + k \quad \text{(C-13)}$$

$$col = (l-1)24 + m \quad \text{(C-14)}$$

In defining the statistical weight matrix $U_{\phi}(j,k,l,i)$ associated with the torsional potential due to the particular sequence of the three bonds j,k,l (where k goes from vertex i-1 to i), the distance $r_{i-2,i+1}$ between residues i-2 to i+1 is considered. If the square of this distance is less than 3, then due to the hard core stearic repulsion,

$$U_{\phi}(j,k,l,i) = 0 \quad \text{(C-15)}$$

If $r^2_{i-2,i+1}=3$, then

$$U_{\phi}(j,k,l,i) = \langle j,k \rangle \langle k,l \rangle \exp\left[-\left(\varepsilon_{\phi}(j,k,l) + 3\varepsilon_{rep}\right)/k_B T\right] \quad \text{(C-16)}$$

If $r^2_{i-2,i+1}=5$, then

$$U_{\phi}(j,k,l,i) = \langle j,k \rangle \langle k,l \rangle \exp\left[-\left(\varepsilon_{\phi}(j,k,l) + \varepsilon_{rep}\right)/k_B T\right]. \quad \text{(C-17)}$$

For all other $r^2_{i-2,i+1}$,

$$U_{\phi}(j,k,l,i) = \langle j,k \rangle \langle k,l \rangle \exp\left[-\left(\varepsilon_{\phi}(j,k,l)\right)/k_B T\right] \quad \text{(C-18)}$$

Thus, local short range repulsions are accounted for in the treatment as well.

For $2<i<l_u$, if l_u is even, and for $2<i\leq l_u$ is odd, then

$$U_i^*(j,k,l,m) = \langle j,k\rangle\langle k,l\rangle\langle l,m\rangle \exp\left(-\left(\varepsilon_{\theta,i-1}(k,l)+\varepsilon_{\theta,i}(l,m)\right)/k_BT\right) U_\phi(j,k,l,i-1)U_\phi(k,l,m,i) \quad \text{(C-19)}$$

If $i=l_u$, and l_u is even then, since vertex i is at the end of the chain, it is necessary to only account for the last bond angle and torsional angle associated with vertex N-1. To make this last matrix conformable with the previous matrices (e.g., vector type 1), an extra bond is appended at the end of the chain, giving:

$$U_{i_u=N}^*(j,k,l,N) = \langle j,k\rangle\langle k,l\rangle\langle l,1\rangle \exp\left(-\varepsilon_{\theta,i-1}(k,l)/k_BT\right) U_\phi(j,k,l,N-1) \quad \text{(C-20)}$$

From the above definitions of U, J and Z, it is seen where the free energy A_D of the denatured state can be determined from the equation:

$$A_D = -k_BT\ln(Z_D).$$

APPENDIX D

```
c       only left handed diamond lattice  vectors can interact
c       revised to include a finer trajectory
c
c       generalized to include other  favoring of torsional potentials
c       uses full hydrophobic hydrophobic interaction matrix
c       based on Miyazawa Jernigan interaction scale
c
c       8/19/89
c       **FIXES THE PROBLEM OF GLYCINES AT POSITIONS 3 AND LENF-2
c       **PRESENT IN ALL PREVIOUS VERSIONS
C
c       ncglyshort.f is a version of ncthermshort.f but which introduces
c       thermalization into the wave displacements
c
c       generates short trajectories
c       like jstherm but it also
c       calculates the number of native contacts
c
c       ****************************************************************
c       SIDECHAINS ONLY A DISTANCE OF THE SQUARE ROOT OF TWO CAN INTERACT
c       all other faces of the sidechain are hard core
c       produces equivalent interaction for 12 and 16 states
c       should produce shifted sq(10) for beta barrel like states
c       with hydrophoblic core
c       program uses setind.f and ergd.f
c
c       ****************************************************************
c       *                                                              *
c       *                    P R O T E I N   201                       *
c       *                    THE NEXT GENERATION                       *
c       *                                                              *
c       ****************************************************************
c
c       WITH GLYCINE (NO SIDE GROUP) CODED AS := 0 (zero) HYDDROPHOBICITY
c       NO GLYCINE ASSUMED ON THE THREE ENDS SEGMENTS. ALLOWS FOR 6 STATE
c
c       PROGRAM SIMULATES SIMPLIFIED MODELS OF GLOBULAR PROTEINS BASED ON
c       THE  " 2 1 0 " LATTICE ALPHA-CARBON REPRESENTATION. INCLUDES SOME
c       DETAILS OF A SEQUENCE DESCRIPTION.  HAS BUILD-IN CHIRALITY OF THE
c       AMINOACIDS.   ASYMETRIC METROPOLIS SCHEME WITH A VARIETY OF LOCAL
c       REARANGEMENTS OF MAIN (AND SIDE GROUPS) CHAIN BACKBONE. EDITED BY
c       AK - FEB. 1989 ST. LOUIS.
c
c       REPULSIVE INTERACTIONS SQRT(5)
c       WITH 'WAVE' MOTIONS, HYDROGEN BONDS, COOPERATIVITY, SIDE GROUPS..
c       THREE (+1) SITE SIDE GROUPS
c       NOTE THAT THIS PROGRAM USES EREP5,EHB,setini,REMOVEG,LOOKG,ERGG
c       setind.f allows for interactions between left handed chirality
c       diamond lattice vector
c       vaxran version
c       ****************************************************************
c       this version of program was created on 5/12/89
c       ****************************************************************
c       4/18/89
```

```
c       constructs the torsional potential in the progarm

c       PHISEQ used
c       ah is the 1./temp in the thermalization step of the waves and
c       rotations
c       at the head of the INPUT file
c       ***********************************************************************

C
C       THE LATERAL TRANSLATION OF A STRING ADDED
C
C       WITH SPECIFFICATION OF THE TORSIONAL POTENTIAL FOR SEQOENCE
C       THIS IS GIVEN IN APH(24,24,24,'LENGTH') ARRAY WHICH HAS TO BE
C       PREPARED AS AN INPUT FILE  FILENAME='PHIPAT' USE AKPHIMAKE
C
C       LIST OF BACKBONE VECTORS - USE FOR ANALYSE OF LOCAL GEOMETRY
C       ...................................................................
C
C       VECTOR NR       1               2  1  0          0 -1  1
C                       2               2  0  1          0  1 -1
C                       3               2 -1  0          0 -1 -1
C       (CODES ALSO     4               2  0 -1          0  1  1
C       FOR DIAMOND
C       LATTICE TL)     5               1  2  0         -1  1  0
C                       6               1  0  2          1 -1  0
C                       7               1 -2  0         -1  0  1
C                       8               1  0 -2          1  0 -1
C
C                       9               0  1  2         -1  0 -1
C                      10               0  2  1          1  0  1
C                      11               0 -1  2         -1 -1  0
C                      12               0  2 -1          1  1  0
C
C                      13               0 -1 -2          F. C. C.
C                      14               0 -2 -1          LATTICE
C                      15               0  1 -2          VECTORS
C                      16               0 -2  1
C
C                      17              -1  2  0
C                      18              -1  0  2
C                      19              -1 -2  0
C                      20              -1  0 -2
C
C       VECTOR NR      21              -2  1  0
C       IS             22              -2  0  1
C       THE            23              -2 -1  0
C       CODE           24              -2  0 -1
C
C       ...................................................................
C
        IMPLICIT INTEGER (I-Z)
```

```
      REAL vaxran
      double precision etot,etot2,cv,anct,ant
      real asumr2,asums2,as2
      LOGICAL GOODC,LOOK
      parameter(ndim=150)
      DIMENSION ASTR(ndim),IDIS(ndim),STATN(ndim)
      DIMENSION astrr(ndim),RIDIS(ndim),RSTATN(ndim),RIHAND(ndim)

      DIMENSION XYZ(ndim,ndim,ndim), X(ndim),Y(ndim),Z(ndim),ihand(ndim)
      DIMENSION VECTOR(-2:2,-2:2,-2:2), VX(24),VY(24),VZ(24)
      DIMENSION ICONF(24,24),GOODC(24,24)
      DIMENSION VECT1(24,24,5),VECT2(24,24,5)
      DIMENSION SIDGR1(24,24),SIDGR2(24,24),SIDGR3(24,24)
      DIMENSION ICA(0:ndim), STLX(13),STLY(13),STLZ(13)
      DIMENSION AC(ndim,20),AM(ndim,ndim),IHYD(ndim),IC6(ndim)
      DIMENSION IC8(ndim),IC10(ndim),IC12(ndim),IC14(ndim),IC16(ndim),IC18(nd
      DIMENSION PRODV(24,24),ICAO(ndim), APH(24,24,24,ndim)
      DIMENSION XNEW(ndim),YNEW(ndim),ZNEW(ndim),INDGL(ndim)
      dimension iflip(20,5),inc(ndim,ndim)
      dimension S1X(24,24)
      dimension S1Y(24,24)
      dimension S1Z(24,24)
      dimension xt(ndim),yt(ndim),zt(ndim)
      DIMENSION AM(ndim,ndim),IHYD(ndim),IC6(ndim),ahyd(ndim,ndim)
C           XYZ - OCCUPANCY LIST WITH SIDE GROUPS (0,-1,INDEX!!!)
C           X, Y, Z - EXPLICITE COORDINATES OF I-LENF BEADS
C           ICONF - R2(VECTOR CODE, VECTOR CODE)
C           ICA - EXPLICITE VECTORS DOWN THE CHAIN
C           APH - ENERGY OF A GIVEN SEQUENCE OF THREE BONDS, DEPENDS
C                 ON CONFORMATION AND THE NUMBER OF THE RESIDUE

      DATA VX /4*2,4*1,8*0,4*-1,4*-2/
      DATA VY /1,0,-1,0,2,0,-2,0,1,2,-1,2,-1,-2,1,-2,2,0,-2,0,1,0,-1,0/
      DATA VZ /0,1,0,-1,0,2,0,-2,2,1,2,-1,-2,-1,-2,1,0,2,0,-2,0,1,0,-1/
C
C     FCC LATTICE VECTORS (AND 000)
      DATA STLX /4*0,-1,1,-1,1,-1,1,-1,1,0/
      DATA STLY /-1,1,-1,1,1,-1,4*0,-1,1,0/
      DATA STLZ /1,-1,-1,1,2*0,1,-1,-1,1,3*0/
C
C      TETRAHEDRAL LATTICE VECTORS
C
      DATA TLX /1,-1,1,-1,1,-1,1,-1/
      DATA TLY /-1,1,-1,1,1,-1,1,-1/
      DATA TLZ /-1,1,1,-1,-1,1,1,-1/
C
C     CODING THE VECTORS TO THE ARRAY
C
      DO XX=-2,2
      DO YY=-2,2
      DO ZZ=-2,2
```

```
VECTOR(XX,YY,ZZ)=0
ENDDO
ENDDO
ENDDO
                VECTOR(2,1,0)=1
                VECTOR(2,0,1)=2
                VECTOR(2,-1,0)=3
                VECTOR(2,0,-1)=4
        VECTOR(1,2,0)=5
        VECTOR(1,0,2)=6
        VECTOR(1,-2,0)=7
        VECTOR(1,0,-2)=8
                VECTOR(0,1,2)=9

                VECTOR(0,2,1)=10
                VECTOR(0,-1,2)=11
                VECTOR(0,2,-1)=12
        VECTOR(0,-1,-2)=13
        VECTOR(0,-2,-1)=14
        VECTOR(0,1,-2)=15
        VECTOR(0,-2,1)=16
                VECTOR(-1,2,0)=17
                VECTOR(-1,0,2)=18
                VECTOR(-1,-2,0)=19
                VECTOR(-1,0,-2)=20
        VECTOR(-2,1,0)=21
        VECTOR(-2,0,1)=22
        VECTOR(-2,-1,0)=23
        VECTOR(-2,0,-1)=24

C       ..................................................................
C       LIST OF CONFORMATIONS - THE SUM OF TWO VECTORS
C       ..................................................................

        DO I=1,24
        DO J=1,24
        ICONF(I,J)=(VX(I)+VX(J))**2+(VY(I)+VY(J))**2+(VZ(I)+VZ(J))**2
        IDOTP=IABS(VX(I)*VX(J)+VY(I)*VY(J)+VZ(I)*VZ(J))
        IF(IDOTP.EQ.5) PRODV(I,J)=1
        ENDDO
        ENDDO

C       THE CODE OF A VECTOR READS  AS CODE=VECTOR(X,Y,Z)  (1 TO 24)
C       AND VICE VERSA COORDINATES READ AS X=VX(CODE).............

C       ..................................................................

C       LIST OF ACCEPTABLE CONFORMATIONS  6-18       (LOGICAL TABLE)
C       ..................................................................
```

```
      DO I=1,24
      DO J=1,24
      IF(ICONF(I,J).LT.6.OR.ICONF(I,J).GT.18) THEN
C                    6,8,10,12,14,16, AND R2=18 ALLOWED
            GOODC(I,J)=.FALSE.
            ELSE
            GOODC(I,J)=.TRUE.
            END IF
      ENDDO
      ENDDO
C
C     .....................................................................
C
C     FLIP-TWIST ARRAY GIVES A DIRECT PREDICTION OF THE NEW CONF. STATE
C     VECT1(I,J,K) GIVES A FIRST VECTOR AFTER JUMP FROM SEQUENCE OF I-J
C     TO NEW STATES (SOMETIMES DEGENERATED) K=1,..5 ( READS AS A CODE )
C     .....................................................................
C
      DO I=1,24

      DO J=1,24
      IF(GOODC(I,J)) THEN
            WX=VX(I)
            WY=VY(I)
            WZ=VZ(I)
            NX=VX(J)
            NY=VY(J)
            NZ=VZ(J)
            VECT1(I,J,1)=J
            VECT1(I,J,4)=J
            VECT1(I,J,5)=J
            VECT2(I,J,1)=I
            VECT2(I,J,4)=I
            VECT2(I,J,5)=I
            ICONA=(ICONF(I,J)-4)/2
            GO TO (6,1,2,3,2,5,2) ICONA
C                                                CONFORMATION R2=6
C                                          FOUR POSSIBILE ARRANGEMENTS
 6          SX=WX+NX
            SY=WY+NY
            SZ=WZ+NZ
            IF(IABS(SX).EQ.2) THEN
                  IF(SY.NE.SZ) THEN
                              WY=-WY
                              WZ=-WZ
                              NZ=-NZ
                              NY=-NY
                              ENDIF
                  WX1=WX
                  WX2=NX
                  WY1=WZ
```

```
                WZ1=WY
                        WY2=NZ
                        WZ2=NY
                GO TO 15
                ENDIF
        IF(IABS(SY).EQ.2) THEN
                IF(SX.NE.SZ) THEN
                                WX=-WX
                                WZ=-WZ
                                NX=-NX
                                NZ=-NZ
                                ENDIF
                WY1=WY
                WY2=NY
                WX1=WZ
                WZ1=WX
                        WX2=NZ
                        WZ2=NX
                GO TO 15
                ENDIF
        IF(IABS(SZ).EQ.2) THEN
                IF(SX.NE.SY) THEN
                                WX=-WX
                                WY=-WY
                                NX=-NX


                                NY=-NY
                                ENDIF
                WZ1=WZ
                WZ2=NZ
                WX1=WY
                WY1=WX
                        WX2=NY
                        WY2=NX
                ENDIF
15      N1=VECTOR(WX1,WY1,WZ1)
        N2=VECTOR(WX2,WY2,WZ2)
        VECT1(I,J,2)=N1
        VECT2(I,J,2)=N2
        VECT1(I,J,3)=N2
        VECT2(I,J,3)=N1
        GO TO 7
C                                                       CONFORMATION R2=5
 1      MX=1
        MY=1
        MZ=1
        IF(IABS(WX).EQ.1) MX=-1
        IF(IABS(WY).EQ.1) MY=-1
        IF(IABS(WZ).EQ.1) MZ=-1
        PX=WX*MX
        PY=WY*MY
```

```
                PZ=WZ*MZ
                I2=VECTOR(PX,PY,PZ)
                LX=NX*MX
                LY=NY*MY
                LZ=NZ*MZ
                J2=VECTOR(LX,LY,LZ)
                VECT1(I,J,2)=I2
                VECT2(I,J,2)=J2
                      VECT1(I,J,4)=I2
                      VECT2(I,J,4)=J2
                      VECT1(I,J,5)=J2
                      VECT2(I,J,5)=I2
                VECT1(I,J,3)=J2
                VECT2(I,J,3)=I2
                GO TO 7
C
C                                                    CONFORMATION R2=10
C                                                    CONFORMATION R2=14
C                                                    CONFORMATION R2=18
 2              VECT1(I,J,2)=J
                VECT2(I,J,2)=I
                VECT1(I,J,3)=J
                VECT2(I,J,3)=I
                GO TO 7
C                                                    CONFORMATION R2=12
 3              TEMPCO=3*WX*NX+2*WY*NY+WZ*NZ
                SX=WX+NX
                SY=WY+NY
                SZ=WZ+NZ
C               TEMPCO=3          X AXIS DIRECTION IN THE ORIGINAL STATE
C                     =2          Y
C                     =1          Z      DIRECTION
                GO TO (13,12,11) TEMPCO
 11             WX1=SX
                WX2=0
                  WZ1=0
                  WZ2=SZ
                    WY1=SY/2
                    WY2=SY/2
                KX1=SX
                KX2=0
                   KY1=0
                   KY2=SY
                    KZ1=SZ/2
                    KZ2=SZ/2
                    GO TO 14
 12             WY1=SY
                WY2=0
                  WZ1=0
                  WZ2=SZ
```

```
          WX1=SX/2
          WX2=SX/2
        KY1=SY
        KY2=0
          KX1=0
          KX2=SX
            KZ1=SZ/2
            KZ2=SZ/2
            GO TO 14
13      WZ1=SZ
        WZ2=0
          WX1=0
          WX2=SX
            WY1=SY/2
            WY2=SY/2
        KZ1=SZ
        KZ2=0
          KY1=0
          KY2=SY
            KX1=SX/2
            KX2=SX/2
14      N1=VECTOR(WX1,WY1,WZ1)
        N2=VECTOR(WX2,WY2,WZ2)
        VECT1(I,J,2)=N1
        VECT2(I,J,2)=N2
        M1=VECTOR(KX1,KY1,KZ1)
        M2=VECTOR(KX2,KY2,KZ2)
        VECT1(I,J,3)=M1
        VECT2(I,J,3)=M2
        VECT1(I,J,4)=N2
        VECT2(I,J,4)=N1
        VECT1(I,J,5)=M2
        VECT2(I,J,5)=M1
        GO TO 7
C                                                    CONFORMATION R2=16
 5      SX=WX+NX
        SY=WY+NY
        SZ=WZ+NZ
        TEMPCO=(3*IABS(SX)+2*IABS(SY)+IABS(SZ))/4
        GO TO (23,22,21) TEMPCO
21      WX1=WX
        WX2=NX
          WY1=WZ
          WY2=NZ
            WZ1=WY
            WZ2=NY
        KX1=WX
        KX2=NX
          KY1=NZ
          KY2=WZ
```

```
                KZ1=NY
                KZ2=WY
                GO TO 24
22            WY1=WY
              WY2=NY
                WX1=WZ
                WX2=NZ
                  WZ1=WX
                  WZ2=NX
              KY1=WY
              KY2=NY
                KX1=NZ
                KX2=WZ
                  KZ1=NX
                  KZ2=WX
                  GO TO 24
23            WZ1=WZ
              WZ2=NZ
                WX1=WY
                WX2=NY
                  WY1=WX
                  WY2=NX
              KZ1=WZ
              KZ2=NZ
                KX1=NY
                KX2=WY
                  KY1=NX
                  KY2=WX
24            N1=VECTOR(WX1,WY1,WZ1)
              N2=VECTOR(WX2,WY2,WZ2)
              VECT1(I,J,2)=N1
              VECT2(I,J,2)=N2
              VECT1(I,J,4)=N2
              VECT2(I,J,4)=N1
              M1=VECTOR(KX1,KY1,KZ1)
              M2=VECTOR(KX2,KY2,KZ2)
              VECT1(I,J,3)=M1
              VECT2(I,J,3)=M2
              VECT1(I,J,5)=M2
              VECT2(I,J,5)=M1
7             CONTINUE
C                                    CONFORMATION IS NOT ACCEPTABLE
              ELSE

                      DO K=1,5
                      VECT1(I,J,K)=0
                      VECT2(I,J,K)=0
                      ENDDO
                      END IF
          ENDDO
          ENDDO
```

```
C
C     ..........................................................
C
C     SIDE GROUPS - EXPLICITE DEFINITION BASED ON CONFORMATION   R2
C     ..........................................................
C
C                  SIDGR1(24,24)  -  CONTAINS CODES OF 110 VECTORS
C                  SIDGR2(24,24)  -  CONTAINS CODES OF 110 VECTORS
C                  SIDGR3(24,24)  -  CONTAINS CODES OF 110 VECTORS
C
      DO I=1,24
      DO J=1,24
            IF(.NOT.GOODC(I,J)) GO TO 40
            X1=VX(I)
            Y1=VY(I)
            Z1=VZ(I)
            X2=VX(J)
            Y2=VY(J)
            Z2=VZ(J)
            ICONA=(ICONF(I,J)-4)/2
            PX=Y1*Z2-Y2*Z1
            PY=X2*Z1-Z2*X1
            PZ=X1*Y2-Y1*X2

                        PX=-PX
                        PY=-PY
                        PZ=-PZ

                  WX=X1-X2
                  WY=Y1-Y2
                  WZ=Z1-Z2
            GO TO (33,32,33,32,31,32,36) ICONA
C                                                    CONFORMATION R2=14
 31   SUMAX=PX
      SUMAY=PY
      SUMAZ=PZ
                        GO TO 39
C                                                    CONFORMATION R2=8
C                                                    CONFORMATION R2=12
C                                                    CONFORMATION R2=16
 32         SUMAX=PX-2*X2
            SUMAY=PY-2*Y2
            SUMAZ=PZ-2*Z2
            GO TO 39
C                                                    CONFORMATION R2=6
C                                                    CONFORMATION R2=10
C
 33   SUMAX=PX+WX
      SUMAY=PY+WY




      SUMAZ=PZ+WZ
```

```
      GO TO 39
C                                                          CONFORMATION R2-18
C
 36           IF(PX*PY.NE.0) THEN
C                                    THE CASE OF DOWN THE AXIS CONFORMATION
      SUMAX=PX
      SUMAY=PY
      SUMAZ=PZ
           GO TO 39
           ENDIF
C                                                 THE CASE OF 330 CONFORMATION

      SUMAX=PX+WX
      SUMAY=PY+WY
      SUMAZ=PZ+WZ
C
C
 39   SUX=ISIGN(1,SUMAX)
      SUY=ISIGN(1,SUMAY)
      SUZ=ISIGN(1,SUMAZ)
           X1=SUX
           X2=SUX
           X3=0
                Y1=SUY
                Y2=0
                Y3=SUY
                     Z1=0
                     Z2=SUZ
                     Z3=SUZ
C
C               GIVES THE CODE OF (STLX,STLY,STLZ)V, VALUE 1,2,..12
           ICODT=9*X1+3*Y1+Z1
           IF(ICODT.LT.0) ICODT=-1-ICODT
           SIDGR1(I,J)=ICODT
           ICODT=9*X2+3*Y2+Z2
           IF(ICODT.LT.0) ICODT=-1-ICODT
           SIDGR2(I,J)=ICODT
           ICODT=9*X3+3*Y3+Z3
           IF(ICODT.LT.0) ICODT=-1-ICODT
           SIDGR3(I,J)=ICODT
c     insert of check for handedness
      x4=(x1+x2+x3)/2
      y4=(y1+y2+y3)/2
      z4=(z1+z2+z3)/2
      S1X(i,j)=x4
      S1Y(i,j)=y4
      S1Z(i,j)=z4

 40   CONTINUE
      ENDDO
      ENDDO


C     INPUT   INPUT  INPUT  INPUT  INPUT  INPUT  INPUT  INPUT   INPUT
C     ------------------------------------------------------------------
```

```
C
C           SET UP OF THE VECTOR REPRESENTATION OF THE CHAIN
C
      OPEN(UNIT=5,FILE='INPUT',STATUS='OLD')
      OPEN(UNIT=10,FILE='FILEDAT',STATUS='OLD')
      OPEN(UNIT=6,FILE='OUTPUT',STATUS='OLD')
      OPEN(UNIT=1,FILE='SEQUENCE',STATUS='OLD')
      OPEN(UNIT=11,FILE='contact',STATUS='OLD')
      OPEN(UNIT=12,FILE='PHISEQH',STATUS='OLD')
      OPEN(UNIT=14,FILE='PHISEQHR',STATUS='OLD')
      OPEN(UNIT=13,FILE='TRACE',STATUS='OLD')
      open(unit=15,file='hydmap',status='old')
      open(unit=16,file='output',status='old')

      READ(10,*) LENF
      LENF1=LENF-1
      LENF2=LENF-2
      AL2=LENF2
      LENF3=LENF-3
      AL3=LENF3
      LENF4=LENF-4
      AL4=LENF4
      AL6=LENF-6
      AL9=LENF-9
      MIX=1
      LENHA=LENF/2



      do i=1,100
      STATN(i)=0.d0
      IDIS(i)=0.d0
      ASTR(i)=0.d0
      IHAND(i)=0.d0
      RSTATN(i)=0.d0
      RIDIS(i)=0.d0
      astrr(i)=0.d0
      RIHAND(i)=0.d0
      do j=1,100
      do k=1,100

      xyz(k,j,i)=0.d0
      end do
      end do
      end do


C
C     **********SEQUENCE READING**********
C
C     **********READING OF TORSIONAL POTENTIALS**********
C
      EXPLICIT CONSTRUCTION OF  APH
      DO LJ=2,LENF1
```

```
      READ(12,*)K,STATN(LJ),IDIS(LJ),ASTR(LJ),IHAND(LJ)

      END DO
c     generalized to include other conformational prefrences
      read(14,*)other
      if(other .eq. 0) go to 542
      do lj=1,other
      READ(14,*)K,RSTATN(k),RIDIS(k),ASTRR(k),RIHAND(k)
      END DO
542   continue
C     **********************SEQUENCE READING*************************
C
C     CAUTION::: THE REVERSE PATTERN IS NOT ALLOWED +K HAS TO BE
C                ASSUMED AS A PREFERENCE FOR A GIVEN STATE


C
C     STATN - R2(I-1,I+1)
C     IDIS - R2(I-1,I+2)
C     ASTR- STRENGTH OF PREFERENCE FOR THE DIHEDRAL ANGLE
C
c     ah plays the role of the thermalization factor
      read(5,*)ah
      WRITE(6,8120)
8120  FORMAT(1X,'  ** THE THREE SIDE GROUP PROGRAM
     * AND GLI glypredict.f full hydrophobic interaction matrix',/,
     *         'uses not necessarily native conf in torsions',/)

      NBGL=0
      INDGL(1)=0
      INDGL(LENF)=0
      DO I=2,LENF1
      INDGL(I)=1
      READ(1,*) K,IC6(I),
     * IC8(I),IC10(I),IC12(I),IC14(I),IC16(I),IC18(I),IHYD(I)
      IF(IHYD(I).EQ.0) THEN
               INDGL(I)=0
               NBGL=NBGL+1
               ENDIF
      ENDDO
C
C     **********************INPUT FILE*******************************
C
      READ(5,*) RANDOM,NCYCLE, PHOT
      READ(5,*) AC6,AC8,AC10,AC12,AC14,AC16,AC18
      READ(5,*) APLPB,BPLPL,CPBPB,AREP,AHB,APHI
      READ(5,*) ATEMP,WAVEL
C
      WRITE(6,8020) RANDOM,NCYCLE,PHOT,WAVEL
```

```
 8020   FORMAT(1X,'  ** THE THREE SIDE GROUP PROGRAM  AND GLI.**',/,
     *          'DIAMOND LATTICE SITES INTERACT ',/,
     *          '**        glypredict with .5 *jernigan       **',
     *  1X,' RANDOM SEED =',I6,'    NUMBER OF CYCLES',2I5,/,
     *  1X, ' MAXIMUM WAVE LENGTH =',I4,/ )
        write(6,8999)ah
 8999   format(1x,' temp/tempthermal =',1f8.4)




        WRITE(6,8021) AC6,AC8,AC10,AC12,AC14,AC16,AC18
 8021   FORMAT(5X,/,3X,' ENERGY OF STATE 6 =',F6.2,/,
     *  3X,' ENERGY OF STATE 8 =',F6.2,/,
     *  3X,' ENERGY OF STATE 10=',F6.2,/,
     *  3X,' ENERGY OF STATE 12=',F6.2,/,
     *  3X,' ENERGY OF STATE 14=',F6.2,/,
     *  3X,' ENERGY OF STATE 16=',F6.2,/,
     *  3X,' ENERGY OF STATE 18=',F6.2,/)
        WRITE(6,8022) APLPB,BPLPL,CPBPB
 8022   FORMAT(3X,' PHIL-PHOB, PHIL-PHIL, PHOB-PHOB    ',4F8.3,/)
        WRITE(6,8024) AREP,AHB,APHI
 8024   FORMAT(3X,' REPULSIVE INT. AND  COOPER.-H-BOND',2F8.3,/
     *  ,3X,' SCALING FACTOR FOR DIHEDRAL ANGLE POTENTIAL',F8.3,/)
        WRITE(6,8023) ATEMP
 8023   FORMAT(1X,/,3X,' TEMPERATURE OF THE SYSTEM =',F8.3,/)
C
C       construction of native contact map
        do i=1,lenf2
        do j=i,lenf1
        inc(i,j)=0.d0
        inc(j,i)=0.d0
        end do
        end do

        read(11,*)ntot
        write(6,2039)ntot
 2039   format(1x,'not=',i3,/,'the native contact pairs are ')
        do i=1,ntot
        read(11,*)j,k
        inc(j,k)=1
        write(6,*)j,k
        end do
C
C       ********** SET THE CURRENT FORCE OF INTERACTIONS **********
C
        APHI=APHI/ATEMP
        AHB=AHB/ATEMP
        AC6=AC6/ATEMP
        AC8=AC8/ATEMP
        AC10=AC10/ATEMP
        AC12=AC12/ATEMP
        AC14=AC14/ATEMP
        AC16=AC16/ATEMP
```

```
      AC18=AC18/ATEMP
      APLPB=APLPB/ATEMP
      BPLPL=BPLPL/ATEMP
      CPBPB=CPBPB/ATEMP
      AREP=AREP/ATEMP

      do i=1,lenf2
      read(15,*)(ahyd(i,j),j=i,lenf2)
C     write(6,*)(ahyd(i,j),j=i,lenf2)
      do j=i,lenf2
      ahyd(j,i)=ahyd(i,j)
      end do
      end do
```

```
            DO I=2,LENF1
            iml=i-1
            DO J=2,lenf1
            jml=j-1
            IF(IABS(I-J).GT.2) THEN
            am(i,j)=ahyd(iml,jml)/atemp
            ELSE
            AM(I,J)=0.
C           A PRIORI NO INTERACTIONS OF SIDE GROUPS WHEN/I-J/<3
            ENDIF
            ENDDO
            ENDDO

C           DO I=2,LENF1
            AC(I,6)=IC6(I)*AC6
            AC(I,8)=IC8(I)*AC8
            AC(I,10)=IC10(I)*AC10
            AC(I,12)=IC12(I)*AC12
            AC(I,14)=IC14(I)*AC14
            AC(I,16)=IC16(I)*AC16
            AC(I,18)=IC18(I)*AC18
            ENDDO

C
C     ***************READING OF TORSIONAL POTENTIALS***************
C
      DO 100 I=1,24
              X1=VX(I)
              Y1=VY(I)
              Z1=VZ(I)
      DO 1200 J=1,24
      IF(GOODC(I,J)) THEN
              X2=VX(J)
              Y2=VY(J)
              Z2=VZ(J)
C                             CROSS PRODUCT OF THE TWO FIRST VECTORS
```

```
              PX=Y1*Z2-Y2*Z1
              PY=Z1*X2-Z2*X1
              PZ=X1*Y2-Y1*X2
            st1=iconf(i,j)
            DO 300 K=1,24
            IF(.NOT.GOODC(J,K)) GO TO 300
              X3=VX(K)
              Y3=VY(K)
              Z3=VZ(K)
              IHAN=PX*X3+PY*Y3+PZ*Z3
            IHAN=SIGN(1,IHAN)
            st2=iconf(j,k)
C.....
C
            DO 401 INDEX=2,LENF2

            B=0.
            aph(i,j,k,index)=0.




            IF(STATN(INDEX).EQ.ST1.AND.STATN(INDEX+1).EQ.ST2) THEN
                        KX=X1+X2+X3
                        KY=Y1+Y2+Y3
                        KZ=Z1+Z2+Z3
                        R2=KX*KX+KY*KY+KZ*KZ
            IF(R2.EQ.IDIS(INDEX).and. ihan .eq. ihand(index))B=ASTR(INDEX)
                        ENDIF
            APH(I,J,K,INDEX)=(B)*APHI
            IF(RSTATN(INDEX).EQ.ST1.AND.RSTATN(INDEX-1).EQ.ST2) THEN
                        KX=X1+X2+X3
                        KY=Y1+Y2+Y3
                        KZ=Z1+Z2+Z3
                        R2=KX*KX+KY*KY+KZ*KZ
            IF(R2.EQ.RIDIS(INDEX).and.ihan.eq.Rihand(index))B=astrR(INDEX)
                        ENDIF
            APH(I,J,K,INDEX)=(B)*APHI
 401        CONTINUE
C.....
C
 300        CONTINUE
            END IF
 1200       CONTINUE
 100        CONTINUE

            ICA(0)=1
C           this is because the simplicity of APH reading, value irrelevant
            ICA(LENF)=1
C
C           **********INITIAL CONFORMATION**********
C
```

```
C                       caution (zero initialization assumed)
      MAX=100
      MID=MAX/2
      SX=0
      SY=0
      SZ=0
      DO I=1,LENF
      READ(10,*) X(I),Y(I),Z(I)
      SX=SX+X(I)
      SY=SY+Y(I)
      SZ=SZ+Z(I)
      ENDDO
              SX=SX/LENF
              SY=SY/LENF
              SZ=SZ/LENF
              XSHIFT=MID-SX
              YSHIFT=MID-SY
              ZSHIFT=MID-SZ
      DO I=1,LENF
      X(I)=X(I)+XSHIFT
      Y(I)=Y(I)+YSHIFT
      Z(I)=Z(I)+ZSHIFT
      ENDDO
              DO I=1,LENF1
              J=I+1

              WX=X(J)-X(I)
              WY=Y(J)-Y(I)
              WZ=Z(J)-Z(I)
              ICA(I)=VECTOR(WX,WY,WZ)
              ENDDO
      CALL setin(XYZ,INDGL(1),X(1),Y(1),Z(1),13,13,13,1)
      CALL setin(XYZ,INDGL(LENF),X(LENF),Y(LENF),Z(LENF),13,13,13,1)
      DO J=2,LENF1
      I=J-1
      II=ICA(I)
      JJ=ICA(J)
      IF(GOODC(II,JJ)) THEN
              S1=SIDGR1(II,JJ)
              S2=SIDGR2(II,JJ)
              S3=SIDGR3(II,JJ)
              CALL setin(XYZ,INDGL(J),X(J),Y(J),Z(J),S1,S2,S3,J)
              ELSE
              WRITE(6,8001) I,J
8001          FORMAT(5X,'WRONG INPUT CHAIN - VECTORS ',2I4)
              GO TO 9000
              END IF
      ENDDO
C

C.....CALCULATION OF THE ENERGY OF INITIAL STATE
```

```
C
      E=0.
      ENERG=0.
      DO J=2,LENF1
      I=J-1
      II=ICA(I)
      JJ=ICA(J)
C                                          ROTATIONAL CONTRIBUTION
      JCONF=ICONF(II,JJ)
      ENERG=ENERG+AC(J,JCONF)
C                                          INTERACTIONS OF SIDE GROUPS

            IX=X(J)+S1X(ii,jj)
            IY=Y(J)+S1Y(ii,jj)
            IZ=Z(J)+S1Z(ii,jj)
            E=E+ERG(XYZ,INDGL(J),AM,IX,IY,IZ,J)
4501  continue
      ENDDO
      ENERG=ENERG+E/2.
C                                          COOPERATIVE AND HYDROGEN BOND
      E=0.
      DO I=2,LENF1
      E=E+EHB(XYZ,ICA,PRODV,X(I),Y(I),Z(I),I,AHB)
      ENDDO
      ENERG=ENERG+E/2

C                                          REPULSIVE INTERACTIONS
      E=0.
      DO I=2,LENF1
      E=E+EREPUL(XYZ,X(I),Y(I),Z(I),1.)
```

```
      ENDDO
C     this is because the implicite symmetry of repulsive interactions
C     which is taken into account in the remainder of the program.

      E=(E-AL3*2.)/2.
      ENERG=ENERG+E*AREP
C
C                                          DIHEDRAL POTENTIAL
      DO J=2,LENF2
      II=ICA(J-1)
      JJ=ICA(J)
      KK=ICA(J+1)
      ENERG=ENERG+APH(II,JJ,KK,J)
      ENDDO

C//////////////////////////////////////////////////
      RN1=RANDOM*2+7531
      RN2=RANDOM*2+8883
      RN3=RANDOM*6+7907
```

```
C     ****************************************************************
C     *                                                              *
C     *                  DYNAMICS OF THE CHAIN                       *
C     *                                                              *
C     ****************************************************************
C
C
C     MAIN CLOCK OF THE ALGORITHM
C
      ICLOCK=1
C
      QROT=0
      QWAVE=0
      QKINK=0
      QEND=0
C
      asumr2=0.
      asums2=0.
      etot=0.d0
      etot2=0.d0
      sxd=0.d0
      syd=0.d0
      szd=0.d0

      anct=0.d0
      ant=0.d0
      write(6,931)
931   format(1x,'iterm=  R2=  AS2=  ENERGY=    native  any contacts')


      DO 7777 ITERM=1,NCYCLE
                              iclock=iclock+1
C
      DO 7700 IDUMI=1,100
                              iclock=iclock+1
c




      DO 7770 IPHCO=1,PHOT
C
      IF(ICLOCK.GT.2000) ICLOCK=ICLOCK-vaxran(rn2)*1000
C
C     ..............LATERAL WAVE DISPLACEMENT.........................
C
c     set up of the thermalization move
      if(vaxran(rn2) .gt. .01) then
            af=1.d0
      else
            af=ah
      end if
      IVA=MOD(ICLOCK,WAVEL)+3
```

```
I=INT(vaxran(rn1)*AL6)+3
IF(I.GT.LENHA) THEN
                IFIRST=I-IVA
                ILAST=I
                ELSE
                IFIRST=I
                ILAST=I+IVA
                ENDIF
        WI=ICA(IFIRST)
        JL=ILAST-1
        WJ=ICA(JL)
        JCONF=ICONF(WI,WJ)
        IF(JCONF.LT.14.OR.JCONF.GT.18) GO TO 7001
        IF(.NOT.GOODC(ICA(IFIRST-1),WJ)) GO TO 7001
        IF(.NOT.GOODC(WJ,ICA(IFIRST+1))) GO TO 7001
        IF(.NOT.GOODC(ICA(ILAST-2),WI)) GO TO 7001
        IF(.NOT.GOODC(WI,ICA(ILAST))) GO TO 7001


C                                                   REMOVE THE STRING
      DO K=IFIRST,ILAST
      II=ICA(K-1)
      KK=ICA(K)
      IKS1=SIDGR1(II,KK)
      IKS2=SIDGR2(II,KK)
      IKS3=SIDGR3(II,KK)
      XJ=X(K)
      YJ=Y(K)
      ZJ=Z(K)
      CALL REMOVE(XYZ,INDGL(K),XJ,YJ,ZJ,IKS1,IKS2,IKS3)
      ENDDO
C                                                   SETIN AND EXCLUDED
C                                                   VOLUME TEST
C                               THE NEW VECTORS
                                ICA(IFIRST)=WJ
                                ICA(JL)=WI

        IFA=IFIRST-1
        XJ=X(IFA)
        YJ=Y(IFA)
        ZJ=Z(IFA)
DO J=IFIRST,ILAST




II=ICA(J-1)

JJJ=ICA(J)
        XJ=XJ+VX(II)
        YJ=YJ+VY(II)
        ZJ=ZJ+VZ(II)
        XNEW(J)=XJ
```

```
                YNEW(J)=YJ
                ZNEW(J)=ZJ
                S1=SIDGR1(II,JJJ)
                S2=SIDGR2(II,JJJ)
                S3=SIDGR3(II,JJJ)
                IF(LOOK(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3)) THEN
C                                                       THEN REMOVE AND TERMINATE
                        IF(J.EQ.IFIRST) GO TO 2004
                        DO K=IFIRST,J-1
                        KK=ICA(K-1)
                        KKK=ICA(K)
                S1=SIDGR1(KK,KKK)
                S2=SIDGR2(KK,KKK)
                S3=SIDGR3(KK,KKK)
                CALL REMOVE(XYZ,INDGL(K),XNEW(K),YNEW(K),ZNEW(K),S1,S2,S3)
                        ENDDO
 2004                           ICA(IFIRST)=WI
                                ICA(JL)=WJ

                        DO I=IFIRST,ILAST
                        II=ICA(I-1)
                        JJJ=ICA(I)

                S1=SIDGR1(II,JJJ)
                S2=SIDGR2(II,JJJ)
                S3=SIDGR3(II,JJJ)

                CALL setin(XYZ,INDGL(I),X(I),Y(I),Z(I),S1,S2,S3,I)
                        ENDDO
                        GO TO 7001
                        ELSE
C                                                               SET NEW BEAD
                CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
                        ENDIF
        ENDDO
C                               THE NEW STRING KEEPS EXCLUDED VOLUME
C
C
C       COMPUTATION OF ENERGY OF THE NEW CONFORMATION AND REMOVE STRING


        ENEW=0.
        ER=0.
        E=0.
        DO J=IFIRST,ILAST
        I=J-1
        II=ICA(I)
        JJ=ICA(J)
                XJ=XNEW(J)




                YJ=YNEW(J)
```

```
              ZJ=ZNEW(J)
              S1=SIDGR1(II,JJ)
              S2=SIDGR2(II,JJ)
              S3=SIDGR3(II,JJ)
            JCONF=ICONF(II,JJ)
            ENEW=ENEW+AC(J,JCONF)+APH(II,JJ,ICA(J+1),J)
C                                           INTERACTIONS OF SIDE GROUPS

              IX=XJ+S1X(ii,jj)
              IY=YJ+S1y(ii,jj)
              IZ=ZJ+S1z(ii,jj)
              E=E+ERG(XYZ,INDGL(J),AM,IX,IY,IZ,J)

C                                           COOPERATIVE AND HYDROGEN BOND
            E=E+EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                           REPULSIVE INTERACTIONS
            ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
                        CALL REMOVE(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3)
            ENDDO
            ENEW=ENEW+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
            ENEW=ENEW+E+ER
C
C
C
C           COMPUTATION OF THE OLD ENERGY AND  SETIN OF THE CHAIN PIECE
C

C             THE OLD VECTORS
              ICA(IFIRST)=WI
              ICA(JL)=WJ
            EOLD=0.
            ER=0.
            E=0.
            DO J=IFIRST,ILAST
            XJ=X(J)
            YJ=Y(J)
            ZJ=Z(J)
            II=ICA(J-1)
            JJJ=ICA(J)
              S1=sIDGR1(II,JJJ)
              S2=SIDGR2(II,JJJ)
              S3=SIDGR3(II,JJJ)
C             s4=sidgr4(ii,jjj)
C           tx=t1x(s4)
C           ty=t1y(s4)
C           tz=t1z(s4)
              CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
C
            JCONF=ICONF(II,JJJ)
            EOLD=EOLD+AC(J,JCONF)+APH(II,JJJ,ICA(J+1),J)
C                                           INTERACTIONS OF SIDE GROUPS

              IX=XJ+S1x(ii,jjj)
              IY=YJ+S1y(ii,jjj)
              IZ=ZJ+S1z(ii,jjj)
```

```
                E=E+ERG(XYZ,INDGL(J),AM,IX,IY,IZ,J)

C                                       COOPERATIVE AND HYDROGEN BOND
        E=E+EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                       REPULSIVE INTERACTIONS
        ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
        ENDDO
        EOLD=EOLD+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
        EOLD=EOLD+E+ER

C
C       METROPOLIS CRITERION
C
        DE=ENEW-EOLD
        IF(EXP(-DE*af).GT.vaxran(rn3)) THEN
C                                                       ACCEPTED
                QROT=QROT+1
                ENERG=ENERG+DE
                        DO J=IFIRST, ILAST
                        II=ICA(J-1)
                        JJ=ICA(J)
                S1=SIDGR1(II,JJ)
                S2=SIDGR2(II,JJ)
                S3=SIDGR3(II,JJ)

                        CALL REMOVE(XYZ,INDGL(J),X(J),Y(J),Z(J),S1,S2,S3)
                        ENDDO
C                               THE NEW VECTORS
                                ICA(IFIRST)=WJ
                                ICA(JL)=WI
                DO J=IFIRST,ILAST
                XJ=XNEW(J)
                YJ=YNEW(J)
                ZJ=ZNEW(J)
                X(J)=XJ
                Y(J)=YJ
                Z(J)=ZJ
                II=ICA(J-1)
                JJ=ICA(J)
                S1=SIDGR1(II,JJ)
                S2=SIDGR2(II,JJ)
                S3=SIDGR3(II,JJ)
                CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
                ENDDO
        ENDIF


 7001   DO 7000 IDUMA=1,LENF4
        ICLOCK=ICLOCK+1
C
        I=INT(vaxran(rn1)*AL4)+2
C               RUNS FROM 2 TO LENF-3 (VECTOR INDEX  RUNS FROM 1 TO LENF-1)
        J=I+1
        KINK=MOD(ICLOCK,5)+1
C               DEFINES KIND OF KINK OF THE  VECTORS I-J
```

```
      IV=ICA(I)

      JV=ICA(J)
      IIV=VECT1(IV,JV,KINK)
      IP=I-1
      IPV=ICA(IP)
      IF(.NOT.GOODC(IPV,IIV)) GO TO 7000
      JN=J+1
      JNV=ICA(JN)
      JJV=VECT2(IV,JV,KINK)
      IF(.NOT.GOODC(JJV,JNV)) GO TO 7000
C
C           CONFORMATION IS OK   - CHECK THE EXCLUDE VOLUME

C                                                  REMOVE THE STRING
      JL=J
      ifirst=i
      ilast=jn
      DO K=IFIRST,ILAST
      II=ICA(K-1)
      KK=ICA(K)
      IKS1=SIDGR1(II,KK)
      IKS2=SIDGR2(II,KK)
      IKS3=SIDGR3(II,KK)
      XJ=X(K)
      YJ=Y(K)
      ZJ=Z(K)
      CALL REMOVE(XYZ,INDGL(K),XJ,YJ,ZJ,IKS1,IKS2,IKS3)
      ENDDO
C                                                  SETIN AND EXCLUDED
C                                                  VOLUME TEST
C                              THE NEW VECTORS
                               ICA(IFIRST)=iiv
                               ICA(JL)=jjv

           IFA=IFIRST-1
           XJ=X(IFA)
           YJ=Y(IFA)
           ZJ=Z(IFA)
      DO J=IFIRST,ILAST
      II=ICA(J-1)
      JJJ=ICA(J)
           XJ=XJ+VX(II)
           YJ=YJ+VY(II)
           ZJ=ZJ+VZ(II)
           XNEW(J)=XJ
           YNEW(J)=YJ
           ZNEW(J)=ZJ
           S1=SIDGR1(II,JJJ)
           S2=SIDGR2(II,JJJ)
```

```
                S3=SIDGR3(II,JJJ)
                IF(LOOK(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3)) THEN
                                                THEN REMOVE AND TERMINATE
C
                        IF(J.EQ.IFIRST) GO TO 2204
                        DO K=IFIRST,J-1
                        KK=ICA(K-1)
                        KKK=ICA(K)

                S1=SIDGR1(KK,KKK)
                S2=SIDGR2(KK,KKK)
                S3=SIDGR3(KK,KKK)
                CALL REMOVE(XYZ,INDGL(K),XNEW(K),YNEW(K),ZNEW(K),S1,S2,S3)
                        ENDDO
2204                            ICA(IFIRST)=IV
                                ICA(JL)=JV

                        DO I=IFIRST,ILAST
                        II=ICA(I-1)
                        JJJ=ICA(I)

                S1=SIDGR1(II,JJJ)
                S2=SIDGR2(II,JJJ)
                S3=SIDGR3(II,JJJ)

        CALL setin(XYZ,INDGL(I),X(I),Y(I),Z(I),S1,S2,S3,I)
                ENDDO
                        GO TO 7000
                        ELSE
                                                        SET NEW BEAD
C
                CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
                        ENDIF
        ENDDO
                                THE NEW STRING KEEPS EXCLUDED VOLUME
C
C
C
C       COMPUTATION OF ENERGY OF THE NEW CONFORMATION AND REMOVE STRING
C

        ENEW=0.
        ER=0.
        E=0.
        DO J=IFIRST,ILAST
        I=J-1
        II=ICA(I)
        JJ=ICA(J)
                XJ=XNEW(J)
                YJ=YNEW(J)
                ZJ=ZNEW(J)
                S1=SIDGR1(II,JJ)
                S2=SIDGR2(II,JJ)
                S3=SIDGR3(II,JJ)
```

```
C                                       ROTATIONAL CONTRIBUTION
      JCONF=ICONF(II,JJ)
      ENEW=ENEW+AC(J,JCONF)+APH(II,JJ,ICA(J+1),J)
C                                       INTERACTIONS OF SIDE GROUPS
            IX=XJ+S1x(ii,jj)
            IY=YJ+S1Y(ii,jj)
            IZ=ZJ+S1z(ii,jj)
            E=E+ERG(XYZ,INDGL(J),AM,IX,IY,IZ,J)

C                                       COOPERATIVE AND HYDROGEN BOND
      E=E+EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                       REPULSIVE INTERACTIONS



      ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
                  CALL REMOVE(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3)
      ENDDO
      ENEW=ENEW+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
      ENEW=ENEW+E+ER
C
C
C
C     COMPUTATION OF THE OLD ENERGY AND SETIN OF THE CHAIN PIECE
C
C           THE OLD VECTORS
            ICA(IFIRST)=IV
            ICA(JL)=JV
      EOLD=0.
      ER=0.
      E=0.
      DO J=IFIRST,ILAST
      XJ=X(J)
      YJ=Y(J)
      ZJ=Z(J)
      II=ICA(J-1)
      JJJ=ICA(J)
            S1=SIDGR1(II,JJJ)
            S2=SIDGR2(II,JJJ)
            S3=SIDGR3(II,JJJ)
C           s4=sidgr4(ii,jjj)
C     tx=tlx(s4)
C     ty=tly(s4)
C     tz=tlz(s4)
            CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
C
      JCONF=ICONF(II,JJJ)
      EOLD=EOLD+AC(J,JCONF)+APH(II,JJJ,ICA(J+1),J)
C                                       INTERACTIONS OF SIDE GROUPS

            IX=XJ+S1x(ii,jjj)
```

```
                IY=YJ+S1Y(ii,jjj)
                IZ=ZJ+S1z(ii,jjj)
                E=E+ERG(XYZ,INDGL(J),AM,IX,IY,IZ,J)

C                                                COOPERATIVE AND HYDROGEN BOND
        E=E+EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                                REPULSIVE INTERACTIONS
        ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
        ENDDO
        EOLD=EOLD+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
        EOLD=EOLD+E+ER

C
C       METROPOLIS CRITERION
C
        DE=ENEW-EOLD
        IF(EXP(-DE).GT.vaxran(rn3)) THEN
                                                                 ACCEPTED
C               iflip(iconf(iv,jv),kink)=iflip(iconf(iv,jv),kink)+1

                QKINK=QKINK+1
                ENERG=ENERG+DE
                        DO J=IFIRST, ILAST
                        II=ICA(J-1)
                        JJ=ICA(J)
                S1=SIDGR1(II,JJ)
                S2=SIDGR2(II,JJ)
                S3=SIDGR3(II,JJ)

                        CALL REMOVE(XYZ,INDGL(J),X(J),Y(J),Z(J),S1,S2,S3)
                        ENDDO
C                               THE NEW VECTORS
                                ICA(IFIRST)=IIV
                                ICA(JL)=JJV
                DO J=IFIRST,ILAST
                XJ=XNEW(J)
                YJ=YNEW(J)
                ZJ=ZNEW(J)
                X(J)=XJ
                Y(J)=YJ
                Z(J)=ZJ
                II=ICA(J-1)
                JJ=ICA(J)
                S1=SIDGR1(II,JJ)
                S2=SIDGR2(II,JJ)
                S3=SIDGR3(II,JJ)
                CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,S1,S2,S3,J)
                ENDDO
        ENDIF

C
```

```
 7000   CONTINUE
c       idummy=1
c       if(idummy .eq. 1) go to 7770
C
C                                END FLIPS (TWO BONDS REARANGEMENTS)
C
C
C               N-TERMINUS (TAIL)
C
        JV3=ICA(3)
 60     NV2=INT(vaxran(rn1)*24.)+1
        IF(.NOT.GOODC(NV2,JV3)) GO TO 60
 61     NV1=INT(vaxran(rn3)*24.)+1
        IF(.NOT.GOODC(NV1,NV2)) GO TO 61
C               CONFORMATION IS OK.  CHECK  THE EXCLUDED VOLUME
        CALL REMOVE(XYZ,INDGL(1),X(1),Y(1),Z(1),13,13,13)
        ICA1=ICA(1)
        ICA2=ICA(2)
        PK21=SIDGR1(ICA1,ICA2)
        PK22=SIDGR2(ICA1,ICA2)
        PK23=SIDGR3(ICA1,ICA2)

c       ****************************
        CALL REMOVE(XYZ,INDGL(2),X(2),Y(2),Z(2),PK21,PK22,PK23)
C               CHECK THE ROTATION OF SIDE GROUP ON THIRD BEAD



c       8/19/89
c        oninvoke if no glycines are here
c
         if(indgl(3) .eq.0) go to 3040
         PK31=SIDGR1(ICA2,JV3)
         PK32=SIDGR2(ICA2,JV3)
         PK33=SIDGR3(ICA2,JV3)
c        ***********************************************
c        ****************************

         SX1=X(3)+STLX(PK31)
         SX2=X(3)+STLX(PK32)
         SX3=X(3)+STLX(PK33)
         SY1=Y(3)+STLY(PK31)
         SY2=Y(3)+STLY(PK32)
         SY3=Y(3)+STLY(PK33)
         SZ1=Z(3)+STLZ(PK31)
         SZ2=Z(3)+STLZ(PK32)
         SZ3=Z(3)+STLZ(PK33)
         XYZ(SX1,SY1,SZ1)=0
         XYZ(SX2,SY2,SZ2)=0
         XYZ(SX3,SY3,SZ3)=0
                        xone=(sx1+sx2+sx3-x(3))/2
                        yone=(sy1+sy2+sy3-y(3))/2
                        zone=(sz1+sz2+sz3-z(3))/2
```

```
                        xyz(xone,yone,zone)=0

              NK31=SIDGR1(NV2,JV3)
              NK32=SIDGR2(NV2,JV3)
              NK33=SIDGR3(NV2,JV3)
c             s4=sidgr4(nv2,jv3)
c             tx=tlx(s4)
c             ty=tly(s4)
c             tz=tlz(s4)
c             **********************
              MX1=X(3)+STLX(NK31)
              MX2=X(3)+STLX(NK32)
              MX3=X(3)+STLX(NK33)
              MY1=Y(3)+STLY(NK31)
              MY2=Y(3)+STLY(NK32)
              MY3=Y(3)+STLY(NK33)
              MZ1=Z(3)+STLZ(NK31)
              MZ2=Z(3)+STLZ(NK32)
              MZ3=Z(3)+STLZ(NK33)
              IF(XYZ(MX1,MY1,MZ1).NE.0) GO TO 64
              IF(XYZ(MX2,MY2,MZ2).NE.0) GO TO 64
              IF(XYZ(MX3,MY3,MZ3).NE.0) GO TO 64
                      mxone=(mx1+mx2+mx3-x(3))/2
                      myone=(my1+my2+my3-y(3))/2
                      mzone=(mz1+mz2+mz3-z(3))/2
                      if(xyz(mxone,myone,mzone).ne.0) go to 64

              XYZ(MX1,MY1,MZ1)=-1
              XYZ(MX2,MY2,MZ2)=-1
              XYZ(MX3,MY3,MZ3)=-1
              xyz(mxone,myone,mzone)=3




c...
c             end of check of sidechain conformation if sidechain there is not
c             a glycine.
3040          continue
              NK21=SIDGR1(NV1,NV2)
              NK22=SIDGR2(NV1,NV2)
              NK23=SIDGR3(NV1,NV2)
c             ****************************
                      WX2=VX(NV2)
                      WY2=VY(NV2)
                      WZ2=VZ(NV2)
              X2=X(3)-WX2
              Y2=Y(3)-WY2
              Z2=Z(3)-WZ2
                      IF(LOOK(XYZ,INDGL(2),X2,Y2,Z2,NK21,NK22,NK23)) GO TO 63
              WX1=VX(NV1)
              WY1=VY(NV1)
              WZ1=VZ(NV1)
                      X1=X2-WX1
```

```
                Y1=Y2-WY1
                Z1=Z2-WZ1
                IF(LOOK(XYZ,INDGL(1),X1,Y1,Z1,13,13,13)) GO TO 63
C
C.....OLD CONFORMATIONAL ENERGY (LOCAL)
C
        IC3=ICONF(ICA2,JV3)
        IC2=ICONF(ICA1,ICA2)
        COLD=AC(2,IC2)+AC(3,IC3)
c       s4=sidgr4(ica1,ica2)
c       tx=tlx(s4)
c       ty=tly(s4)
c       tz=tlz(s4)
c       PK23=SIDGR3(ICA1,ICA2)
c       ipk21=ihan1(ica1,ica2)
        QX1=X(2)+slx(ica1,ica2)
        Qy1=y(2)+sly(ica1,ica2)
        Qz1=z(2)+slz(ica1,ica2)

        SuX1=X(3)+SlX(ica2,jv3)
        Suy1=y(3)+Sly(ica2,jv3)
        Suz1=z(3)+Slz(ica2,jv3)

        EOLD=COLD
     *           +ERG(XYZ,INDGL(3),AM,SuX1,SuY1,SuZ1,3)

c    *           +ERG(XYZ,INDGL(3),AM,SuX3,SuY3,SuZ3,3)
     *           +ERG(XYZ,INDGL(2),AM,QX1,QY1,QZ1,2)


     *           +APH(ICA1,ICA2,JV3,2)+APH(ICA2,JV3,ICA(4),3)
     *           +EREPUL(XYZ,X(2),Y(2),Z(2),AREP)
     *           +EHB(XYZ,ICA,PRODV,X(3),Y(3),Z(3),3,AHB)
     *           +EHB(XYZ,ICA,PRODV,X(2),Y(2),Z(2),2,AHB)
```

```
C
C.....NEW CONFORMATIONAL ENERGY (LOCAL)
C
                ICA(1)=NV1
                ICA(2)=NV2

        IC3=ICONF(NV2,JV3)
        IC2=ICONF(NV1,NV2)
        CNEW=AC(2,IC2)+AC(3,IC3)
c       ****************************
c       s4=sidgr4(nv1,nv2)
c       tx=tlx(s4)
c       ty=tly(s4)
```

```
c       tz=tlz(s4)

        LX1=X2+S1x(nv1,nv2)
        Ly1=y2+S1y(nv1,nv2)
        Lz1=z2+S1z(nv1,nv2)

        MuX1=X(3)+S1X(nv2,jv3)
        Muy1=y(3)+S1y(nv2,jv3)
        Muz1=z(3)+S1z(nv2,jv3)


        ENEW=CNEW
     *           +ERG(XYZ,INDGL(3),AM,muX1,muY1,MuZ1,3)

     *           +ERG(XYZ,INDGL(2),AM,LX1,LY1,LZ1,2)

     *           -APH(NV1,NV2,JV3,2)+APH(NV2,JV3,ICA(4),3)
     *           -EREPUL(XYZ,X2,Y2,Z2,AREP)
     *           -EHB(XYZ,ICA,PRODV,X(3),Y(3),Z(3),3,AHB)
     *           +EHB(XYZ,ICA,PRODV,X2,Y2,Z2,2,AHB)
c.....METROPOLIS CRITERION
c
                DE=ENEW-EOLD
                IF(EXP(-DE).LT.vaxran(rn3)) GO TO 63
                ENERG=ENERG+DE
c
c               SET-IN THE NEW CONFORMATION OF THE TAIL
        X(1)=X1
        Y(1)=Y1
        Z(1)=Z1
        X(2)=X2
        Y(2)=Y2
        Z(2)=Z2
                CALL setin(XYZ,INDGL(1),X1,Y1,Z1,13,13,13,1)
        CALL SETIN(XYZ,INDGL(2),X2,Y2,Z2,NX21,NX22,NX23,2)
                QEND=QEND+1
                GO TO 79
c
c               SET-IN THE OLD CONFORMATION OF THE TAIL
63      if(indgl(3) .eq. 0) go to 641
        XYZ(MX1,MY1,MZ1)=0
        XYZ(MX2,MY2,MZ2)=0
        XYZ(MX3,MY3,MZ3)=0

        xyz(mxone,myone,mzone)=0

 64     XYZ(SX1,SY1,SZ1)=-1
        XYZ(SX2,SY2,SZ2)=-1
        XYZ(SX3,SY3,SZ3)=-1
```

```
      xyz(xone,yone,zone)=3
641    continue
             ICA(1)=ICA1
             ICA(2)=ICA2
             CALL setin(XYZ,INDGL(1),X(1),Y(1),Z(1),13,13,13,1)
      CALL SETIN(XYZ,INDGL(2),X(2),Y(2),Z(2),PK21,PK22,PK23,2)
C
C             C-TERMINUS (HEAD)
C
 79   JV3=ICA(LENF3)
 80   NV2=INT(vaxran(rn1)*24.)+1
      IF(.NOT.GOODC(JV3,NV2)) GO TO 80
 81   NV1=INT(vaxran(rn2)*24.)+1
      IF(.NOT.GOODC(NV2,NV1)) GO TO 81
C             CONFORMATION IS OK.  CHECK  THE EXCLUDED VOLUME
      CALL REMOVE(XYZ,INDGL(LENF),X(LENF),Y(LENF),Z(LENF),13,13,13)
      ICA2=ICA(LENF2)
      ICA1=ICA(LENF1)
      PK21=SIDGR1(ICA2,ICA1)
      PK22=SIDGR2(ICA2,ICA1)
      PK23=SIDGR3(ICA2,ICA1)
C
      IIII=INDGL(LENF1)
      CALL REMOVE(XYZ,IIII,X(LENF1),Y(LENF1),Z(LENF1),PK21,PK22,PK23)
C             CHECK THE ROTATION OF SIDE GROUP ON THIRD BEAD
      if(indgl(lenf2) .eq. 0) go to 6045
      PK31=SIDGR1(JV3,ICA2)
      PK32=SIDGR2(JV3,ICA2)
      PK33=SIDGR3(JV3,ICA2)

      SX1=X(LENF2)+STLX(PK31)
      SY1=Y(LENF2)+STLY(PK31)
      SZ1=Z(LENF2)+STLZ(PK31)
      SX2=X(LENF2)+STLX(PK32)
      SY2=Y(LENF2)+STLY(PK32)
      SZ2=Z(LENF2)+STLZ(PK32)
      SX3=X(LENF2)+STLX(PK33)
      SY3=Y(LENF2)+STLY(PK33)
      SZ3=Z(LENF2)+STLZ(PK33)
      XYZ(SX1,SY1,SZ1)=0
      XYZ(SX2,SY2,SZ2)=0
      XYZ(SX3,SY3,SZ3)=0
                     xone=(sx1+sx2+sx3-x(lenf2))/2
                     yone=(sy1+sy2+sy3-y(lenf2))/2
                     zone=(sz1+sz2+sz3-z(lenf2))/2
                     xyz(xone,yone,zone)=0

      NK31=SIDGR1(JV3,NV2)
      NK32=SIDGR2(JV3,NV2)




      NK33=SIDGR3(JV3,NV2)
```

```
            MX1=X(LENF2)+STLX(NK31)
            MY1=Y(LENF2)+STLY(NK31)
            MZ1=Z(LENF2)+STLZ(NK31)
            MX2=X(LENF2)+STLX(NK32)
            MY2=Y(LENF2)+STLY(NK32)
            MZ2=Z(LENF2)+STLZ(NK32)
            MX3=X(LENF2)+STLX(NK33)
            MY3=Y(LENF2)+STLY(NK33)
            MZ3=Z(LENF2)+STLZ(NK33)

            IF(XYZ(MX1,MY1,MZ1).NE.0) GO TO 84
            IF(XYZ(MX2,MY2,MZ2).NE.0) GO TO 84
            IF(XYZ(MX3,MY3,MZ3).NE.0) GO TO 84
                    mxone=(mx1+mx2+mx3-x(lenf2))/2
                    myone=(my1+my2+my3-y(lenf2))/2
                    mzone=(mz1+mz2+mz3-z(lenf2))/2
                    if(xyz(mxone,myone,mzone).ne.0) go to 84
            XYZ(MX1,MY1,MZ1)=-1
            XYZ(MX2,MY2,MZ2)=-1
            XYZ(MX3,MY3,MZ3)=-1
            xyz(mxone,myone,mzone)=lenf2
c....
6045        continue
            NK21=SIDGR1(NV2,NV1)
            NK22=SIDGR2(NV2,NV1)
            NK23=SIDGR3(NV2,NV1)
                    WX2=VX(NV2)
                    WY2=VY(NV2)
                    WZ2=VZ(NV2)
            X2=X(LENF2)+WX2
            Y2=Y(LENF2)+WY2
            Z2=Z(LENF2)+WZ2
                    IF(LOOK(XYZ,IIII,X2,Y2,Z2,NK21,NK22,NK23)) GO TO 83
            WX1=VX(NV1)
            WY1=VY(NV1)
            WZ1=VZ(NV1)
                    X1=X2+WX1
                    Y1=Y2+WY1
                    Z1=Z2+WZ1
                    IF(LOOK(XYZ,INDGL(LENF),X1,Y1,Z1,13,13,13)) GO TO 83

c
c.....OLD CONFORMATIONAL ENERGY (LOCAL)
c
            IC3=ICONF(JV3,ICA2)
            IC2=ICONF(ICA2,ICA1)
            COLD=AC(LENF1,IC2)+AC(LENF2,IC3)
c           s4=sidgr4(ica2,ica1)
c           tx=tlx(s4)
c           ty=tly(s4)
c           tz=tlz(s4)
            QX1=X(lenf1)+S1X(ica2,ica1)
            Qy1=y(lenf1)+S1y(ica2,ica1)
            Qz1=z(lenf1)+S1z(ica2,ica1)
```

```
      SuX1=X(LENF2)+S1X(jv3,ica2)
      Suy1=y(LENF2)+S1y(jv3,ica2)
      Suz1=z(LENF2)+S1z(jv3,ica2)


c     QX1=X(LENF1)+STLX(PK21)*
c     QY1=Y(LENF1)+STLY(PK21)
c     QZ1=Z(LENF1)+STLZ(PK21)
c     QX2=X(LENF1)+STLX(PK22)
c     QY2=Y(LENF1)+STLY(PK22)
c     QZ2=Z(LENF1)+STLZ(PK22)
c     QX3=X(LENF1)+STLX(PK23)
c     QY3=Y(LENF1)+STLY(PK23)
c     QZ3=Z(LENF1)+STLZ(PK23)
      ECLD=COLD
     *          -ERG(XYZ,INDGL(LENF2),AM,SuX1,suY1,suZ1,LENF2)


     *          +APH(ICA(LENF4),JV3,ICA2,LENF3)
     *          +APH(JV3,ICA2,ICA1,LENF2)
     *          +ERG(XYZ,IIII,AM,QX1,QY1,QZ1,LENF1)


     *          +EREPUL(XYZ,X(LENF1),Y(LENF1),Z(LENF1),AREP)
     *          +EHB(XYZ,ICA,PRODV,X(LENF2),Y(LENF2),Z(LENF2),LENF2,AHB)
     *          +EHB(XYZ,ICA,PRODV,X(LENF1),Y(LENF1),Z(LENF1),LENF1,AHB)

C.....NEW CONFORMATIONAL ENERGY (LOCAL)
C
            ICA(LENF1)=NV1
            ICA(LENF2)=NV2

      IC3=ICONF(JV3,NV2)
      IC2=ICONF(NV2,NV1)
      CNEW=AC(LENF1,IC2)+AC(LENF2,IC3)

      LX1=X2+s1x(nv2,nv1)
      Ly1=y2+s1y(nv2,nv1)
      Lz1=z2+s1z(nv2,nv1)


      MuX1=X(lenf2)+S1x(jv3,nv2)
      Muy1=y(lenf2)+S1y(jv3,nv2)
      Muz1=z(lenf2)+S1z(jv3,nv2)



c     LX1=X2+STLX(NK21)
c     LY1=Y2+STLY(NK21)
c     LZ1=Z2+STLZ(NK21)
c     LX2=X2+STLX(NK22)
c     LY2=Y2+STLY(NK22)
c     LZ2=Z2+STLZ(NK22)
```

```
c       LX3=X2-STLX(NK23)

c       LY3=Y2+STLY(NK23)
c       LZ3=Z2+STLZ(NK23)
        ENEW=CNEW
     *          +ERG(XYZ,INDGL(LENF2),AM,muX1,muY1,muZ1,LENF2)

     *          -APH(ICA(LENF4),JV3,NV2,LENF3)

     *          +APH(JV3,NV2,NV1,LENF2)
     *          -ERG(XYZ,IIII,AM,LX1,LY1,LZ1,LENF1)

     *          -EREPUL(XYZ,X2,Y2,Z2,AREP)
     *          -EHB(XYZ,ICA,PRODV,X(LENF2),Y(LENF2),Z(LENF2),LENF2,AHB)
     *          -EHB(XYZ,ICA,PRODV,X2,Y2,Z2,LENF1,AHB)

C
C.....METROPOLIS CRITERION
C
                DE=ENEW-EOLD
                IF(EXP(-DE).LT.vaxran(rn3)) GO TO 83
                ENERG=ENERG+DE
C
C               SET-IN THE NEW CONFORMATION OF THE HEAD
        X(LENF)=X1
        Y(LENF)=Y1
        Z(LENF)=Z1
        X(LENF1)=X2
        Y(LENF1)=Y2
        Z(LENF1)=Z2
                CALL setin(XYZ,INDGL(LENF),X1,Y1,Z1,13,13,13,1)
        CALL SETIN(XYZ,IIII,X2,Y2,Z2,NK21,NK22,NK23,LENF1)
                QEND=QEND+1
                GO TO 7007
C
C               SET-IN THE OLD CONFORMATION OF THE TAIL
83      if(indgl(lenf2) .eq. 0) go to 675
        XYZ(MX1,MY1,MZ1)=0
        XYZ(MX2,MY2,MZ2)=0
        XYZ(MX3,MY3,MZ3)=0
        xyz(mxone,myone,mzone)=0

 84     XYZ(SX1,SY1,SZ1)=-1
        XYZ(SX2,SY2,SZ2)=-1
        XYZ(SX3,SY3,SZ3)=-1
        xyz(xone,yone,zone)=lenf2
675     continue
```

```
            ICA(LENF1)=ICA1
            ICA(LENF2)=ICA2
      CALL setin(XYZ,INDGL(LENF),X(LENF),Y(LENF),Z(LENF),13,13,13,1)
      CALL SETIN(XYZ,IIII,X(LENF1),Y(LENF1),Z(LENF1),PK21,PK22,PK23,LENF1)
C
C     WAVE LIKE MOTION OF THE CHAIN FRAGMENT, VARIOUS CONFORMATIONS
C
 7007 I=INT(AL9*vaxran(rn2))+3
      if( vaxran(rn3) .gt. .01) then
      af=1.d0
      else
      af =ah
      end if
C
C     I+2 IS THE CENTRAL BEAD OF THE PIECE TO BE CUT-OFF
C     JJ - IS THE CENTRAL ONE OF THE PIECE TO BE CONSTRUCTED
C     SEARCH FOR U-SHAPED (OF VARIOUS WIDTH) CONFORMATIONS
C
      IV2=ICA(I)
      IV5=ICA(I+3)
      VX2=VX(IV2)
      VX5=VX(IV5)
      IF(VX2.NE.-VX5) GO TO 7770
      VY2=VY(IV2)
      VY5=VY(IV5)
      IF(VY2.NE.-VY5) GO TO 7770
      VZ2=VZ(IV2)
      VZ5=VZ(IV5)
      IF(VZ2.NE.-VZ5) GO TO 7770
C                                     LOOK FOR THE SECOND END
      IVA=MOD(ICLOCK,WAVEL)
      MIX=-MIX
      JJ=I+2+MIX*(5+IVA)
      IF(JJ.LT.4.OR.JJ.GT.LENF3) GO TO 7770
C                                     ACCEPTED DOWN THE CHAIN CHOICE
C                                     I-END CONSTRUCTION   (CUT-OFF)
      IV3=ICA(I+2)
      IV4=ICA(I+1)
C                                     KINK PERFORMEDED (KINK==1)
      IV1=ICA(I-1)
      I4=I+4
      IV6=ICA(I4)
      IF(GOODC(IV1,IV3).AND.GOODC(IV4,IV6)) GO TO 200
C                                     ELSE TRY KINK FLIP OF THE TOP

            INV3=VECT1(IV3,IV4,KINK)
            IV4=VECT2(IV3,IV4,KINK)
            IV3=INV3
            IF(.NOT.GOODC(IV1,IV3)) GO TO 7770
```

```
                IF(.NOT.GOODC(IV4,IV6)) GO TO 7770
C                                                  CONSTRUCT THE NEW JJ- END
 200    J1=JJ-1
        JV1=ICA(J1)
        JV2=ICA(JJ)
        JVL=ICA(JJ-2)
        J3=JJ+1
        JVP=ICA(J3)
 201    V=INT(vaxran(rn1)*24.)+1
        IF(.NOT.GOODC(JVL,V)) GO TO 201
        WVX=VX(V)
        WVY=VY(V)

        WVZ=VZ(V)
        VM=VECTOR(-WVX,-WVY,-WVZ)
        IF(.NOT.GOODC(VM,JVP)) GO TO 201
C                                          TOP OF THE JJ-END CNSTRUCTED
                DO KINK=1,5
                JN1=VECT1(JV1,JV2,KINK)
                IF(GOODC(V,JN1)) THEN
                        JN2=VECT2(JV1,JV2,KINK)
                        IF(GOODC(JN2,VM)) GO TO 202
                        END IF
                ENDDO
        GO TO 7770
C
C       MODIFFICATION OF THE BOND STRING ARRAY ICA. STORE THE OLD ONE
C
 202    IF(MIX.GT.0) THEN
                IFIRST=I
                ILAST=J3
                ELSE
                IFIRST=J1
                ILAST=I4
                ENDIF

        DO J=IFIRST-1,ILAST
        ICAO(J)=ICA(J)
        ENDDO
C
                IF(MIX.GT.0) THEN
                        ICA(I)=IV3
                        ICA(I+1)=IV4
                        DO J=I4,JJ-2
                        ICA(J-2)=ICAO(J)
                        ENDDO
                        ICA(JJ)=VM
                        ICA(J1)=JN2
                        ICA(J1-1)=JN1
                        ICA(J1-2)=V
```

```
            ELSE
                    ICA(I4-1)=IV4
                    ICA(I4-2)=IV3
                    DO J=J3,I-1
                    ICA(J-2)=ICAO(J)
                    ENDDO
                    ICA(J1)=V
                    ICA(JJ)=JN1
                    ICA(J3)=JN2
                    ICA(J3+1)=VM
            END IF
C                                                   REMOVE THE STRING
        DO K=IFIRST,ILAST
        II=ICAO(K-1)
        KK=ICAO(K)
        IKS1=SIDGR1(II,KK)
        IKS2=SIDGR2(II,KK)
        IKS3=SIDGR3(II,KK)
        XJ=X(K)
```

```
        YJ=Y(K)
        ZJ=Z(K)
        CALL REMOVE(XYZ,INDGL(K),XJ,YJ,ZJ,IKS1,IKS2,IKS3)
        ENDDO
C
C                                                   SETIN AND EXCLUDED
C                                                   VOLUME TEST
            IFA=IFIRST-1

            XJ=X(IFA)
            YJ=Y(IFA)
            ZJ=Z(IFA)
        DO J=IFIRST,ILAST
        II=ICA(J-1)
        JJJ=ICA(J)
            XJ=XJ+VX(II)
            YJ=YJ+VY(II)
            ZJ=ZJ+VZ(II)
            XNEW(J)=XJ
            YNEW(J)=YJ
            ZNEW(J)=ZJ
        IKS1=SIDGR1(II,JJJ)
        IKS2=SIDGR2(II,JJJ)
        IKS3=SIDGR3(II,JJJ)

                    IF(LOOK(XYZ,INDGL(J),XJ,YJ,ZJ,IKS1,IKS2,IKS3)) THEN
C                                                   THEN REMOVE AND TERMINATE
                    IF(J.EQ.IFIRST) GO TO 204
                    DO K=IFIRST,J-1
                    KK=ICA(K-1)
                    KKK=ICA(K)
                IKS1=SIDGR1(KK,KKK)
```

```
            IKS2=SIDGR2(KK,KKK)
            IKS3=SIDGR3(KK,KKK)
      CALL REMOVE(XYZ,INDGL(K),XNEW(K),YNEW(K),ZNEW(K),IKS1,IKS2,IKS3)
            ENDDO
  204               DO I=IFIRST,ILAST
                    ICA(I)=ICAO(I)
                    II=ICA(I-1)


                    JJJ=ICA(I)
                    IKS1=SIDGR1(II,JJJ)
                    IKS2=SIDGR2(II,JJJ)
                    IKS3=SIDGR3(II,JJJ)
      CALL setin(XYZ,INDGL(I),X(I),Y(I),Z(I),IKS1,IKS2,IKS3,I)
                    ENDDO
                    GO TO 7770
                    ELSE
C                                                       SET NEW BEAD
            CALL SETIN(XYZ,INDGL(J),XJ,YJ,ZJ,IKS1,IKS2,IKS3,J)
                    ENDIF
      ENDDO
C                           THE NEW STRING KEEPS EXCLUDED VOLUME
C
C
C


C     COMPUTATION OF ENERGY OF THE NEW CONFORMATION AND REMOVE STRING
C

      ENEW=0.
      ER=0.
      E=0.
      DO J=IFIRST,ILAST
      I=J-1
      II=ICA(I)
      JJ=ICA(J)
            XJ=XNEW(J)
            YJ=YNEW(J)
            ZJ=ZNEW(J)
      IKS1=SIDGR1(II,JJ)
      IKS2=SIDGR2(II,JJ)
      IKS3=SIDGR3(II,JJ)


C                                       ROTATIONAL CONTRIBUTION
      JCONF=ICONF(II,JJ)
      ENEW=ENEW+AC(J,JCONF)+APH(II,JJ,ICA(J-1),J)
C                                       INTERACTIONS OF SIDE GROUPS
            IX1=XJ+S1x(ii,jj)
            Iy1=yJ+S1y(ii,jj)
            Iz1=zJ+S1z(ii,jj)
```

```
                E=E+ERG(XYZ,INDGL(J),AM,IX1,IY1,IZ1,J)

C                                          COOPERATIVE AND HYDROGEN BOND
        E=E+EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                          REPULSIVE INTERACTIONS
        ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
                        CALL REMOVE(XYZ,INDGL(J),XJ,YJ,ZJ,IKS1,IKS2,IKS3)
        ENDDO
        ENEW=ENEW+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
        ENEW=ENEW+E+ER
C
C
C
C       COMPUTATION OF THE OLD ENERGY AND SETIN OF THE CHAIN PIECE
C
                        DO J=IFIRST,ILAST
                        I=ICA(J)
                        ICA(J)=ICAO(J)
                        ICAO(J)=I
                        ENDDO
C                       NEW ICA STORED IN ICAO AT THIS POINT
        EOLD=0.
        ER=0.
        E=0.
        DO J=IFIRST,ILAST
        XJ=X(J)
        YJ=Y(J)
        ZJ=Z(J)
        II=ICA(J-1)
        JJJ=ICA(J)









                        IKS1=SIDGR1(II,JJJ)
                        IKS2=SIDGR2(II,JJJ)
                        IKS3=SIDGR3(II,JJJ)
C       s4=sidgr4(ii,jjj)
C       tx=tlx(s4)
C       ty=tly(s4)
C       tz=tlz(s4)
                CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,IKS1,IKS2,IKS3,J)
C
        JCONF=ICONF(II,JJJ)
        EOLD=EOLD+AC(J,JCONF)+APH(II,JJJ,ICA(J+1),J)
C                                          INTERACTIONS OF SIDE GROUPS
                IX1=XJ+S1x(ii,jjj)
                Iy1=yJ+S1y(ii,jjj)
                Iz1=zJ+S1z(ii,jjj)
                E=E+ERG(XYZ,INDGL(J),AM,IX1,IY1,IZ1,J)


C                                          COOPERATIVE AND HYDROGEN BOND
```

```
      E=E-EHB(XYZ,ICA,PRODV,XJ,YJ,ZJ,J,AHB)
C                                        REPULSIVE INTERACTIONS
      ER=ER+EREPUL(XYZ,XJ,YJ,ZJ,AREP)
      ENDDO
      EOLD=EOLD+APH(ICA(IFIRST-2),ICA(IFA),ICA(IFIRST),IFA)
      EOLD=EOLD+E+ER

C
C     METROPOLIS CRITERION
C
      DE=ENEW-EOLD
      IF(EXP(-DE*af).GT.vaxran(rn3)) THEN
C                                                    ACCEPTED
            QWAVE=QWAVE+1
            ENERG=ENERG+DE
                  DO J=IFIRST, ILAST
                  II=ICA(J-1)
                  JJ=ICA(J)
                  IKS1=SIDGR1(II,JJ)
                  IKS2=SIDGR2(II,JJ)
                  IKS3=SIDGR3(II,JJ)
            CALL REMOVE(XYZ,INDGL(J),X(J),Y(J),Z(J),IKS1,IKS2,IKS3)
                  ENDDO
            DO J=IFIRST,ILAST
            XJ=XNEW(J)
            YJ=YNEW(J)
            ZJ=ZNEW(J)
            X(J)=XJ
            Y(J)=YJ
            Z(J)=ZJ
            II=ICAO(J-1)
            JJ=ICAO(J)
                  IKS1=SIDGR1(II,JJ)
                  IKS2=SIDGR2(II,JJ)
                  IKS3=SIDGR3(II,JJ)
            CALL setin(XYZ,INDGL(J),XJ,YJ,ZJ,IKS1,IKS2,IKS3,J)
            ICA(J)=ICAO(J)

                  ENDDO
      ENDIF
C
7770  CONTINUE
C
C                                 OPTIONAL NORMALISATION OF THE COORDINATES
      SX=0
      SY=0
      SZ=0
      DO I=1,LENF
      SX=SX+X(I)
      SY=SY+Y(I)
      SZ=SZ+Z(I)
```

```
        zt(i)=z(i)-szc
        end do
        write(13,*)(xt(i),yt(i),zt(i),i=1,lenf)

        R2=(X(LENF)-X(1))**2+(Y(LENF)-Y(1))**2+(Z(LENF)-Z(1))**2
        asumr2=asumr2+r2
        etot2=etot2+energ*energ
        etot=etot+energ
        AS2=0.
        SX=0
        SY=0
        SZ=0
        DO I=1,LENF
        SX=SX+X(I)
        SY=SY+Y(I)
        SZ=SZ+Z(I)
        ENDDO
C                                          CENTRE OF GRAVITY COORDINATES
               ASX=FLOAT(SX)/LENF
               ASY=FLOAT(SY)/LENF
               ASZ=FLOAT(SZ)/LENF

        DO I=1,LENF

        BX=(ASX-X(I))**2
        BY=(ASY-Y(I))**2
        BZ=(ASZ-Z(I))**2
        AS2=AS2+BX+BY+BZ
        ENDDO
        AS2=AS2/LENF
        asums2=asums2+as2
c       insertion of the native contact pairs

        nt=0.d0
        nct=0.
        do 1400 i=2,lenf2
        k=i+1
        ii=ica(i-1)
        iii=ica(i)
        SX1=slx(ii,iii)-x(i)
        Sy1=sly(ii,iii)-y(i)
        Sz1=slz(ii,iii)+z(i)
               DO 1400 J=K,LENF1
c it is not counting the nearest1 down-the-chain neighbours, which may be
c usefull for some purposes ..........................................
               if(iabs(i-j).eq.1) go to 1400
               iR2=(X(J)-X(I))**2+(Y(J)-Y(I))**2-(Z(J)-Z(I))**2
               IF(iR2.GT.18) GO TO 1400
               II=ICA(J-1)




               III=ICA(J)
```

```
                Kx1=s1X(II,III)+X(J)
                KY1=S1Y(II,III)+Y(J)
                KZ1=S1Z(II,III)+Z(J)
          R11=(SX1-KX1)**2+(SY1-KY1)**2+(SZ1-KZ1)**2
          IF(R11.EQ.2) then
          nct=nct+inc(i,j)
          nt=nt+1
          end if
1400      CONTINUE
          ant=ant+nt
          anct=anct+nct
          WRITE(6,8009) ITERM, R2, AS2, ENERG,nct,nt
8009      FORMAT(2X,2I5,F8.2,F10.4,3x,i3,2x,i3)

C
 7777     CONTINUE
C
 9000                                        CONTINUE
          REWIND(UNIT=10)
          WRITE(10,8000) LENF
          DO I=1,LENF
          WRITE(10,8000) X(I),Y(I),Z(I)
          ENDDO

c         DO I=2,LENF1
          WRITE(6,8000) I,X(I),Y(I),Z(I),ICA(I),ICONF(ICA(I-1),ICA(I))
c         ENDDO


C         ACCEPTANCE RATIOS FOR VARIOUS MOVES
          FKINK=FLOAT(QKINK)/FLOAT(NCYCLE*PHOT)/AL4/100.
          FWAVE=FLOAT(QWAVE)/FLOAT(NCYCLE*PHOT)/100.
          FROT=FLOAT(QROT)/FLOAT(NCYCLE*PHOT)/100.
          FEND=FLOAT(QEND)/FLOAT(NCYCLE*PHOT)/200.
          etot=etot/ncycle
          etot2=etot2/ncycle
          cv=etot2-etot*etot
          asumr2=asumr2/ncycle
          asums2=asums2/ncycle

          anct=anct/ncycle
          ant=ant/ncycle
          write(6,9942)etot,etot2,cv,asumr2,asums2,anct,ant
9942      format(1x,'<E>=',1PD15.8,5X,'<E2>=',1Pd15.8,5X,'CV=',1pd15.8,/,
     *       'mean-square-end to end vector=',1pd15.8,/,
     *             '<S2>=',1pd15.8,/, 'native contacts=',1pd15.8,/,
     *             ' number of contacts=',1pd15.8,/)

          write(6,8012)
8012      format(1x,'      fkink=      fend =    fwave=     frot=')
          WRITE(6,8002) FKINK,FEND,FWAVE,FROT
C
C         DETAILED ANALYSIS OF THE CHAIN STRUCTURE

C
```

```
      write(16,181) atemp,etot,cv,asumr2,asums2,anct,ant
181   format(1x,1f8.3,2x,6(1f8.3,2x))

      WRITE(6,8004)
8004  FORMAT(1X,//,8X,'VECTOR1   VECTOR2',8x,'SIDE 1/2/3',6x,'HANDENES',/)

      DO I=2,LENF1
      II=ICA(I-1)
      JJ=ICA(I)
      KK=ICA(I+1)

      Icj=ICONF(II,JJ)
            SID1=SIDGR1(II,JJ)
            SID2=SIDGR2(II,JJ)
            SID3=SIDGR3(II,JJ)


      WX1=VX(II)
      WY1=VY(II)
      WZ1=VZ(II)
      WX2=VX(JJ)
      WY2=VY(JJ)
      WZ2=VZ(JJ)
      WX3=VX(KK)
      WY3=VY(KK)
      WZ3=VZ(KK)
      R3=(WX1+WX2+WX3)**2+(WY1+WY2+WY3)**2+(WZ1+WZ2+WZ3)**2
      W1X=(S1X(ii,jj))*INDGL(I)
      W1y=(S1y(ii,jj))*INDGL(I)
      W1z=(S1z(ii,jj))*INDGL(I)
c     specification of the non interactions fcc sites


      W2X=st1x(sid1)*INDGL(I)
      W2y=st1y(sid1)*INDGL(I)
      W2z=st1z(sid1)*INDGL(I)


      W3X=st1x(sid2)*INDGL(I)
      W3y=st1y(sid2)*INDGL(I)
      W3z=st1z(sid2)*INDGL(I)


      W4X=st1x(sid3)*INDGL(I)
      W4y=st1y(sid3)*INDGL(I)
      W4z=st1z(sid3)*INDGL(I)


      IHX=(WY1*WZ2-WY2*WZ1)*INDGL(I)
      IHY=(WX2*WZ1-WZ2*WX1)*INDGL(I)
      IHZ=(WX1*WY2-WY1*WX2)*INDGL(I)
      IH1=ISIGN(1,(IHX*W1X+IHY*W1Y+IHZ*W1Z))

      WRITE(6,8003) I,WX1,WY1,WZ1,WX2,WY2,WZ2,
     *  W1X,W1Y,W1Z,W2X,W2Y,W2Z,W3X,W3Y,W3Z,IH1,icj,r3
```

```
      ENDDO
C                                          CENTRE OF GRAVITY COORDINATES
            ASX=FLOAT(SX)/LENF
            ASY=FLOAT(SY)/LENF
            ASZ=FLOAT(SZ)/LENF
            XSHIFT=MID-ASX
            YSHIFT=MID-ASY
            ZSHIFT=MID-ASZ
      IF((XSHIFT**2+YSHIFT**2+ZSHIFT**2).GT.30) THEN
C                                                        NORMALISATION
            CALL REMOVE(XYZ,INDGL(1),X(1),Y(1),Z(1),13,13,13)
            CALL REMOVE(XYZ,INDGL(LENF),X(LENF),Y(LENF),Z(LENF),13,13,13)
            DO I=2,LENF1
            II=ICA(I-1)
            JJ=ICA(I)
            SID1=SIDGR1(II,JJ)
            SID2=SIDGR2(II,JJ)
            SID3=SIDGR3(II,JJ)
            CALL REMOVE(XYZ,INDGL(I),X(I),Y(I),Z(I),SID1,SID2,SID3)
            ENDDO
            DO I=1,LENF
            X(I)=X(I)+XSHIFT
            Y(I)=Y(I)+YSHIFT
            Z(I)=Z(I)+ZSHIFT
            ENDDO
            sxd=sxd-xshift
            syd=syd-yshift
            szd=szd-zshift

            CALL setin(XYZ,INDGL(1),X(1),Y(1),Z(1),13,13,13,1)
            CALL setin(XYZ,INDGL(LENF),X(LENF),Y(LENF),Z(LENF),13,13,13,1)
            DO I=2,LENF1
            II=ICA(I-1)
            JJ=ICA(I)
            SID1=SIDGR1(II,JJ)
            SID2=SIDGR2(II,JJ)
            SID3=SIDGR3(II,JJ)

            CALL setin(XYZ,INDGL(I),X(I),Y(I),Z(I),SID1,SID2,SID3,1)
            ENDDO
            END IF
C
7700  CONTINUE


C


      write(13,*)iterm,energ,sxd,syd,szd
      do i=1,lenf
      xt(i)=x(i)+sxd
      yt(i)=y(i)+syd
```

```
      ENDDO

 8003 FORMAT(1X,I4,X,3I3,X,3I3,2X,3I2,X,3I2,X,3I2,2X,I2,x,i3,x,i3)
 8002 FORMAT(1X,//,5X,5F10.6)
      write(6,8010)
 8010 format(1x,/,5x,50(1h-),/)
 8000 FORMAT(3X,5I4,I6)
      do i=6,18,2
      write(6,8005) i,iflip(i,1),iflip(i,2),iflip(i,3),iflip(i,4),
     * iflip(i,5)
      enddo
 8005 format(1x,i5,5i8)
c
c     testl of occupancy - a direct one
      lenfo7=lenf*7
      lenf23=lenf2-NBGL
      write(6,8006) lenf, lenfo7, lenf23,nbgl
 8006 format(1x,/,5x,'lenf  7*lenf  lenf-2 -nbgl  ngbl',4i6,/)
      isi=0
      ione=0
      ioc=0
      do xx=1,max
      do yy=1,max
      do zz=1,max
      point=xyz(xx,yy,zz)
      if(point.ne.0) then

            if(point.gt.0) then
                  isi=isi-1
                  else
                  if(point.eq.-1) ione=ione-1
                        ioc=ioc-1
                  endif
            endif
      enddo
      enddo
      enddo
c writing of the backbone and side groups coordinates - without the
c central (inert) bead
c
c     do  i=2,lenf2
c     ii=ica(i-1)
c     iii=ica(i)
c     SX1=stlLX(SIDGR1(II,III))+X(I)
c     SY1=stlLY(SIDGR1(II,III))+Y(I)
c     SZ1=stlLZ(SIDGR1(II,III))+Z(I)
c     SX2=stlLX(SIDGR2(II,III))+X(I)
c     SY2=stlLY(SIDGR2(II,III))-Y(I)
c     SZ2=stlLZ(SIDGR2(II,III))+Z(I)
c     SX3=stlLX(SIDGR3(II,III))+X(I)
c     SY3=stlLY(SIDGR3(II,III))+Y(I)
```

```
c       SZ3=stlLZ(SIDGR3(II,III))+Z(I)
c       write(6,420) x(i),y(i),z(i),sx1,sy1,sz1,sx2,sy2,sz2,
c     * sx3,sy3,sz3
c 420   format(5x,4(2x,3i4))
c       enddo
        ioc=ioc-3*(lenf2-nbgl)

        ione=(ione-14)/3 -2
c       there are 3 -1 per side chain that is not a glycine
c       let us count the number of excess minus ones

        write(6,8007) ione, ioc,isi
 8007   format(1x,//,1X,'L-GLY, occupancy and side groups ',3i6,//,
     *  5x,'************  contact map ************',/)

        do 400 i=2,lenf2
        k=i+1
        ii=ica(i-1)
        iii=ica(i)
c       s4=sidgr4(ii,iii)
c       tx=tlx(s4)
c       ty=tly(s4)
c       tz=tlz(s4)
c       ih1=ihan1(ii,iii)
c       ih2=ihan2(ii,iii)
c       ih3=ihan3(ii,iii)

        SX1=s1x(ii,iii)+x(i)
        Sy1=s1y(ii,iii)+y(i)
        Sz1=s1z(ii,iii)+z(i)


                DO 400 J=K,LENF1
c it is not counting the nearest1 down-the-chain neighbours, which may be
c usefull for some purposes .....................................
                if(iabs(i-j).eq.1) go to 400
                R2=(X(J)-X(I))**2+(Y(J)-Y(I))**2+(Z(J)-Z(I))**2
                IF(R2.GT.18) GO TO 400
                II=ICA(J-1)
                III=ICA(J)
                KX1=s1X(II,III)+X(J)
                KY1=S1Y(II,III)+Y(J)
                KZ1=S1Z(II,III)+Z(J)

        R11=(SX1-KX1)**2+(SY1-KY1)**2+(SZ1-KZ1)**2
        mult=0

        IF(R11.EQ.2) MULT=MULT+1
                IF(MULT.EQ.0) GO TO 400
                IF(am(i,j) .gt. 0) THEN
```

```
              WRITE(6,410) I,J,am(i,j)
              elseIF(am(i,j).lt.0) THEN
                     WRITE(6,411) I,J,am(i,j)
                     else
                     WRITE(6,412) I,J,am(i,j)
                     ENDIF
400     CONTINUE
 410    FORMAT(5X,I3,' and',I3,' residues are repulsive ',1f10.4)
 411    FORMAT(3X,'**',I3, ' and',I3,' are attractive ',1f10.4)
412     format(5x,i3,'and',i3,'are inert ',1f10.4)

        CLOSE(UNIT=1)
        CLOSE(UNIT=2)









        CLOSE(UNIT=5)
        CLOSE(UNIT=6)
        CLOSE(UNIT=10)

        stOP

        END
```

```
function vaxran(iseed)
equivalence (iyfl,yfl2)
data mask,mask2/x'3f000000',x'3f800000'/
iseed=iseed*69069 + 1
nseed=rshift(iseed,8)
if(iseed.lt.0) then
 iyfl= mask2+nseed
 vaxran=yfl2
else
 iyfl=mask+nseed
 vaxran=yfl2-.5
endif
return
end
```

```
C
C       ..............SIDE *3 ...GLYCINE.......................
C       REMOVES THE CLUSTER (RESIDUE + SIDE GROUP)
        SUBROUTINE REMOVE (XYZ,INDGL,JX,JY,JZ,ID1,ID2,ID3)
        INTEGER XYZ(150,150,150),STLX(13),STLY(13),STLZ(13)
C       FCC LATTICE VECTORS (AND 000)
        DATA STLX /4*0,-1,1,-1,1,-1,1,-1,1,0/
        DATA STLY /-1,1,-1,1,1,-1,4*0,-1,1,0/
        DATA STLZ /1,-1,-1,1,2*0,1,-1,-1,1,3*0/
C
              IF(INDGL.EQ.0) GO TO 88
        IX=JX+STLX(ID1)
        IY=JY+STLY(ID1)
        IZ=JZ+STLZ(ID1)
        XYZ(IX,IY,IZ)=0
        IIX=JX+STLX(ID2)
        IIY=JY+STLY(ID2)
        IIZ=JZ+STLZ(ID2)
        XYZ(IIX,IIY,IIZ)=0
        IIIX=JX+STLX(ID3)
        IIIY=JY+STLY(ID3)
        IIIZ=JZ+STLZ(ID3)
        XYZ(IIIX,IIIY,IIIZ)=0
              LX=(IX+IIX+IIIX-JX)/2
              LY=(IY+IIY+IIIY-JY)/2
              LZ=(IZ+IIZ+IIIZ-JZ)/2
              XYZ(LX,LY,LZ)=0
88      XYZ(JX,JY,JZ)=0
        IXL=JX-1
        XYZ(IXL,JY,JZ)=0
        IXP=JX+1
        XYZ(IXP,JY,JZ)=0
        IYL=JY-1
        XYZ(JX,IYL,JZ)=0
        IYP=JY+1
        XYZ(JX,IYP,JZ)=0
        IZL=JZ-1
        XYZ(JX,JY,IZL)=0
        IZP=JZ+1
        XYZ(JX,JY,IZP)=0
        RETURN
        END
```

```
C       .................SIDE *3 ..glycine.....................
C       THIS SUBROUTINE SETS -INDEX TO THE EXCLUDED VOLUME ENVELOPE
C       AND INDEX=2,.... LENF1 AT THE SIDE GROUP POSITION. BOTH THE
C       TERMINUSES ARE CODED -1 (IT IS USED IN ENERGY CALCULATIONS)
C
C       ..........................................................
C
C       ONLY THE FCC LATTICE VECTORS ARE ALLOWED TO INTERACT
C       subroutine setind.f
C       includes check for handedness so that all interacting points
C       are left handed
        SUBROUTINE SETIN (XYZ,INDGL,JX,JY,JZ,ID1,ID2,ID3,IND)
        INTEGER XYZ(150,150,150),STLX(13),STLY(13),STLZ(13),INDGL
C       FCC LATTICE VECTORS (AND 000)
        DATA STLX /4*0,-1,1,-1,1,-1,1,-1,1,0/
        DATA STLY /-1,1,-1,1,1,-1,4*0,-1,1,0/
        DATA STLZ /1,-1,-1,1,2*0,1,-1,-1,1,3*0/
              if(indgl.eq.0) go to 88
        IX=JX+STLX(ID1)
        IY=JY+STLY(ID1)
        IZ=JZ+STLZ(ID1)
        XYZ(IX,IY,IZ)=-1
        IIX=JX+STLX(ID2)
        IIY=JY+STLY(ID2)
        IIZ=JZ+STLZ(ID2)
        XYZ(IIX,IIY,IIZ)=-1
        IIIX=JX+STLX(ID3)
        IIIY=JY+STLY(ID3)
        IIIZ=JZ+STLZ(ID3)
        XYZ(IIIX,IIIY,IIIZ)=-1
              LX=(IX+IIX+IIIX-JX)/2
              LY=(IY+IIY+IIIY-JY)/2
              LZ=(IZ+IIZ+IIIZ-JZ)/2
              XYZ(LX,LY,LZ)=ind
 88     XYZ(JX,JY,JZ)=-IND
        IXL=JX-1
        XYZ(IXL,JY,JZ)=-IND
        IXP=JX+1
        XYZ(IXP,JY,JZ)=-IND
        IYL=JY-1
        XYZ(JX,IYL,JZ)=-IND
        IYP=JY+1
        XYZ(JX,IYP,JZ)=-IND
        IZL=JZ-1
        XYZ(JX,JY,IZL)=-IND
        IZP=JZ+1
        XYZ(JX,JY,IZP)=-IND
        RETURN
        END
```

```
C
C       .....................SIDE *3 ...glycine.....................
C       CHECK OF OCCUPANCY - ENTIRE CLUSTER (RESIDUE+SIDE GROUP)
        FUNCTION LOOK(XYZ,INDGL,JX,JY,JZ,ID1,ID2,ID3)
        LOGICAL LOOK
        INTEGER XYZ(150,150,150),STLX(13),STLY(13),STLZ(13)
C       FCC LATTICE VECTORS (AND 000)
        DATA STLX /4*0,-1,1,-1,1,-1,1,-1,1,0/
        DATA STLY /-1,1,-1,1,1,-1,4*0,-1,1,0/
        DATA STLZ /1,-1,-1,1,2*0,1,-1,-1,1,3*0/
              LOOK=.FALSE.
C
              IF(INDGL.EQ.0) GO TO 88
        IX=JX+STLX(ID1)
        IY=JY+STLY(ID1)
        IZ=JZ+STLZ(ID1)
        IF(XYZ(IX,IY,IZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
        IIX=JX+STLX(ID2)
        IIY=JY+STLY(ID2)
        IIZ=JZ+STLZ(ID2)
        IF(XYZ(IIX,IIY,IIZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
        IIIX=JX+STLX(ID3)
        IIIY=JY+STLY(ID3)
        IIIZ=JZ+STLZ(ID3)
        IF(XYZ(IIIX,IIIY,IIIZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
        LX=(IX+IIX+IIIX-JX)/2
        LY=(IY+IIY+IIIY-JY)/2
        LZ=(IZ+IIZ+IIIZ-JZ)/2
        IF(XYZ(LX,LY,LZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
C
 88     IF(XYZ(JX,JY,JZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
        IXL=JX-1
        IF(XYZ(IXL,JY,JZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
              ENDIF
        IXP=JX+1
        IF(XYZ(IXP,JY,JZ).NE.0) THEN
              LOOK=.TRUE.
              RETURN
```

```
            ENDIF

IYL=JY-1
IF(XYZ(JX,IYL,JZ).NE.0) THEN
        LOOK=.TRUE.
        RETURN
        ENDIF
IYP=JY+1
IF(XYZ(JX,IYP,JZ).NE.0) THEN
        LOOK=.TRUE.
        RETURN
        ENDIF
IZL=JZ-1
IF(XYZ(JX,JY,IZL).NE.0) THEN
        LOOK=.TRUE.
        RETURN
        ENDIF
IZP=JZ+1
IF(XYZ(JX,JY,IZP).NE.0) LOOK=.TRUE.
RETURN
END
```

```
C       ..............side 3  .......glycine.....................
C       THIS FUNCTION COMPUTES THE STRENGTH OF INTERACTIONS BETWEEN THE
C       SIDE GROUPS - only the nearest neighbours r=1, for ak102gly.f
c       all interactions are at a distance 2
c
c       program setind.f 5/12/89
        FUNCTION ERG(XYZ,INDGL,AM,KSX,KSY,KSZ,J)
        DIMENSION AM(150,150)
        INTEGER XYZ(150,150,150),P1,P2,P3,P4,P5,P6,p7,p8,p9
        integer p10,p11,p12

        ERG=0.
        IF(INDGL.EQ.0) RETURN

        IX=KSX-1
        JX=KSX+1
        IY=KSY-1
        JY=KSY+1
        IZ=KSZ-1
        JZ=KSZ+1
C
c       vectors in the z plane
        P1=XYZ(JX,jy,KSZ)
        IF(P1.GT.0) ERG=ERG+AM(P1,J)
        P2=XYZ(jX,iY,KSZ)
        IF(P2.GT.0) ERG=ERG+AM(P2,J)
        P3=XYZ(iX,jy,KSZ)
        IF(P3.GT.0) ERG=ERG+AM(P3,J)
        p4=XYZ(iX,iY,KSZ)
        IF(p4.GT.0) ERG=ERG+AM(p4,J)

c       vectors in the x plane
        p5=XYZ(KSX,JY,jZ)
        IF(p5.GT.0) ERG=ERG+AM(p5,J)
        p6=XYZ(KSX,IY,jZ)
        IF(p6.GT.0) ERG=ERG+AM(p6,J)
        p7=XYZ(KSX,JY,iZ)
        IF(p7.GT.0) ERG=ERG+AM(p7,J)
        p8=XYZ(KSX,IY,iz)
        IF(p8.GT.0) ERG=ERG+AM(p8,J)

C       VECTORS IN THE Y PLANE
        P9=XYZ(IX,KSY,JZ)
        IF(P9.GT.0) ERG=ERG+AM(P9,J)
        P10=XYZ(IX,KSY,IZ)
        IF(P10.GT.0) ERG=ERG+AM(P10,J)
        P11=XYZ(JX,KSY,JZ)
        IF(P11.GT.0) ERG=ERG+AM(P11,J)
        P12=XYZ(JX,KSY,IZ)
        IF(P12.GT.0) ERG=ERG+AM(P12,J)
        RETURN
        END
```

```
C       repulsion only to r2-5
C
C       THIS FUNCTION COMPUTES THE STRENGTH OF REPULSIVE INTERACTIONS
c
        FUNCTION EREPUL(XYZ,X,Y,Z,AREP)
        INTEGER XYZ(150,150,150),X,Y,Z
        DATA L0 /-1/
        I=0
        IX=X-1
        JX=X+1
        IY=Y-1
        JY=Y+1
        IZ=Z-1
        JZ=Z+1
c                                           fcc lattice
        IF(XYZ(IX,IY,Z).LT.L0) I=I+1
        IF(XYZ(IX,JY,Z).LT.L0) I=I+1
        IF(XYZ(JX,IY,Z).LT.L0) I=I+1
        IF(XYZ(JX,JY,Z).LT.L0) I=I+1
              IF(XYZ(X,IY,IZ).LT.L0) I=I+1
              IF(XYZ(X,IY,JZ).LT.L0) I=I+1
              IF(XYZ(X,JY,IZ).LT.L0) I=I+1
              IF(XYZ(X,JY,JZ).LT.L0) I=I+1
        IF(XYZ(IX,Y,IZ).LT.L0) I=I+1
        IF(XYZ(IX,Y,JZ).LT.L0) I=I+1
        IF(XYZ(JX,Y,IZ).LT.L0) I=I+1
        IF(XYZ(JX,Y,JZ).LT.L0) I=I+1
        EREPUL=I*AREP
        RETURN
        END
```

```
C
C       HYDROGEN BONDING AND "COOPERATIVITY" (BETA AND ALPHA MOTIFFS)
        FUNCTION EHB(XYZ,ICA,PRODV,IX,IY,IZ,ID,AHB)
        INTEGER XYZ(150,150,150),ICA(0:150),PRODV(24,24)
        DATA L0 /-1/
        I=0
        IXL=IX-3
        IXP=IX+3
        IYL=IY-3
        IYP=IY+3
        IZL=IZ-3
        IZP=IZ+3
        IC1=ICA(ID-1)
        IC2=ICA(ID)
        IF(XYZ(IXL,IY,IZ).LT.L0) THEN
                IDD=-XYZ(IXL,IY,IZ)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF

        IF(XYZ(IXP,IY,IZ).LT.L0) THEN
                IDD=-XYZ(IXP,IY,IZ)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF
C
        IF(XYZ(IX,IYL,IZ).LT.L0) THEN
                IDD=-XYZ(IX,IYL,IZ)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF
C
        IF(XYZ(IX,IYP,IZ).LT.L0) THEN
                IDD=-XYZ(IX,IYP,IZ)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF
C
        IF(XYZ(IX,IY,IZL).LT.L0) THEN
                IDD=-XYZ(IX,IY,IZL)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF
C
        IF(XYZ(IX,IY,IZP).LT.L0) THEN
                IDD=-XYZ(IX,IY,IZP)
                IN1=ICA(IDD-1)
                IN2=ICA(IDD)
        I=I+PRODV(IC1,IN1)+PRODV(IC1,IN2)+PRODV(IC2,IN1)+PRODV(IC2,IN2)
                ENDIF
```

APPENDIX E

SAMPLE INPUT

```
.25  0.25  0.25  0.34  0.25  0.34  0.25   ← Weights for states 6,8,10,12,14,16,18
1.   0.25  0.75  6.0   -0.15 -0.6          Repulsive potential weight.
                                           Dihedral (tortional/ rotational) angle weight.
                                           Hydrogen bond (bond angle) parameter.
0.35       4        Size of kink jump
```

States

Residue	6	8	10	12	14	16	18	Hydrophobicity	
2	1	1	1	0	1	1	1	-1	} Bond angle preferences for various states.
3	1	1	1	0	1	1	1	-1	
4	1	1	1	0	1	1	1	-1	
.									
.									
.									
10	1	1	0	1	1	1	-1		
11	1	1	1	1	0	1	1		
.									
.									
.									
31	1	1	1	1	0	1	1	0	← Glycine
.									
.									
.									
43	1	1	1	1	0	1	1	1	
.									
.									
.									
n									

2	16	37	1	1	} Dihedral (tortional/ rotational) angles for sequence.
3	16	37	1	1	
.					
.					
.					

Residue	6	8	10	12	14	16	18	Hydrophobicity
10	10	21	1.5	1				
.								
.								
.								
31	14	11	1.5	-1				
.								
.								
.								
43	14	29	1.5	-1				
.								
.								
.								
n								

PHIL-PHOB, PHIL-PHIL, PHOB-PHOB	1.000	0.250	-0.750
REPULSIVE INT. AND COOPER. +H-BOND	6.000	-0.150	
SCALING FACTOR FOR DIHEDRAL ANGLE POTENTIAL		-0.600	

APPENDIX E

SAMPLE TERTIARY INTERACTION TABLE

APPENDIX E

SAMPLE TERTIARY INTERACTION TABLE

1 = cys	6 = val	11 = thr	16 = asp
2 = met	7 = tryp	12 = ser	17 = his
3 = phe	8 = tyr	13 = gln (glutamine)	18 = arg
4 = ile	9 = ala	14 = asn	19 = lys
5 = len	10 = gly	15 = glu (glutonic acid)	20 = pro

cys interactions

ahyd(1,1)=-5.44
ahyd(1,2)=-5.05
ahyd(1,3)=-5.63
ahyd(1,4)=-5.03
ahyd(1,5)=-5.03
ahyd(1,6)=-4.46
ahyd(1,7)=-4.76
ahyd(1,8)=-3.89
ahyd(1,9)=-3.38
ahyd(1,10)=-3.16
ahyd(1,11)=-2.88
ahyd(1,12)=-2.86
ahyd(1,13)=-2.73
ahyd(1,14)=-2.59
ahyd(1,15)=-2.08
ahyd(1,16)=-2.66
ahyd(1,17)=-3.63
ahyd(1,18)=-2.70
ahyd(1,19)=-1.54
ahyd(1,20)=-2.92

phe interactions

ahyd(3,3)=-6.85
ahyd(3,4)=-6.39
ahyd(3,5)=-6.26
ahyd(3,6)=-5.75
ahyd(3,7)=-6.02
ahyd(3,8)=-4.95
ahyd(3,9)=-4.36
ahyd(3,10)=-3.72
ahyd(3,11)=-3.76
ahyd(3,12)=-3.56
ahyd(3,13)=-3.30
ahyd(3,14)=-3.55
ahyd(3,15)=-3.51
ahyd(3,16)=-3.31
ahyd(3,17)=-4.61
ahyd(3,18)=-3.54
ahyd(3,19)=-2.83
ahyd(3,20)=-3.73

leu

ahyd(5,5)=-5.79
ahyd(5,6)=-5.38
ahyd(5,7)=-5.50
ahyd(5,8)=-4.26
ahyd(5,9)=-3.96
ahyd(5,10)=-3.43
ahyd(5,11)=-3.43
ahyd(5,12)=-3.16
ahyd(5,13)=-3.09
ahyd(5,14)=-2.99
ahyd(5,15)=-2.91
ahyd(5,16)=-2.59
ahyd(5,17)=-3.84
ahyd(5,18)=-3.15
ahyd(5,19)=-2.63
ahyd(5,20)=-3.06

valine

ahyd(6,6)=-4.94
ahyd(6,7)=-5.05
ahyd(6,8)=-4.05
ahyd(6,9)=-3.62
ahyd(6,10)=-3.06
ahyd(6,11)=-2.95
ahyd(6,12)=-2.79
ahyd(6,13)=-2.67
ahyd(6,14)=-2.36
ahyd(6,15)=-2.56
ahyd(6,16)=-2.25
ahyd(6,17)=-3.38
ahyd(6,18)=-2.78
ahyd(6,19)=-1.95
ahyd(6,20)=-2.96

met interactions

ahyd(2,2)=-6.06
ahyd(2,3)=-6.68
ahyd(2,4)=-6.33
ahyd(2,5)=-6.01
ahyd(2,6)=-5.52
ahyd(2,7)=-6.37
ahyd(2,8)=-4.92
ahyd(2,9)=-3.99
ahyd(2,10)=-3.75
ahyd(2,11)=-3.73
ahyd(2,12)=-3.55
ahyd(2,13)=-3.17
ahyd(2,14)=-3.50
ahyd(2,15)=-3.19
ahyd(2,16)=-2.90
ahyd(2,17)=-3.31
ahyd(2,18)=-3.49
ahyd(2,19)=-3.11
ahyd(2,20)=-4.11

ile interactions

ahyd(4,4)=-6.22
ahyd(4,5)=-6.17
ahyd(4,6)=-5.58
ahyd(4,7)=-5.64
ahyd(4,8)=-4.63
ahyd(4,9)=-4.41
ahyd(4,10)=-3.65
ahyd(4,11)=-3.74
ahyd(4,12)=-3.43
ahyd(4,13)=-3.22
ahyd(4,14)=-2.99
ahyd(4,15)=-3.23
ahyd(4,16)=-2.91
ahyd(4,17)=-3.76
ahyd(4,18)=-3.33
ahyd(4,19)=-2.70
ahyd(4,20)=-3.47

tryp

ahyd(7,7)=-5.42
ahyd(7,8)=-4.44
ahyd(7,9)=-3.93
ahyd(7,10)=-3.37
ahyd(7,11)=-3.31
ahyd(7,12)=-2.95
ahyd(7,13)=-3.16
ahyd(7,14)=-3.11
ahyd(7,15)=-2.94
ahyd(7,16)=-2.91
ahyd(7,17)=-4.02
ahyd(7,18)=-3.56
ahyd(7,19)=-2.49
ahyd(7,20)=-3.66

APPENDIX E (Cont.)

Sample Tertiary Interaction Table (Cont.)

tyr
ahyd(8,8)=-3.55
ahyd(8,9)=-2.85
ahyd(8,10)=-2.50
ahyd(8,11)=-2.48
ahyd(8,12)=-2.30
ahyd(8,13)=-2.53
ahyd(8,14)=-2.47
ahyd(8,15)=-2.42
ahyd(8,16)=-2.25
ahyd(8,17)=-3.33
ahyd(8,18)=-2.75
ahyd(8,19)=-2.01
ahyd(8,20)=-2.80
++++++++++++++++++
ala
ahyd(9,9)=-2.51
ahyd(9,10)=-2.15
ahyd(9,11)=-2.15
ahyd(9,12)=-1.89
ahyd(9,13)=-1.70
ahyd(9,14)=-1.44
ahyd(9,15)=-1.51
ahyd(9,16)=-1.57
ahyd(9,17)=-2.09
ahyd(9,18)=-1.50
ahyd(9,19)=-1.10
ahyd(9,20)=-1.81
++++++++++++++++++
ahyd(10,10)=-2.17
ahyd(10,11)=-2.03
ahyd(10,12)=-1.70
ahyd(10,13)=-1.54
ahyd(10,14)=-1.56
ahyd(10,15)=-1.22
ahyd(10,16)=-1.62
ahyd(10,17)=-1.94
ahyd(10,18)=-1.68
ahyd(10,19)=-0.84
ahyd(10,20)=-1.72
++++++++++++++++++

thr
ahyd(11,11)=-1.72
ahyd(11,12)=-1.59
ahyd(11,13)=-1.59
ahyd(11,14)=-1.51
ahyd(11,15)=-1.45
ahyd(11,16)=-1.66
ahyd(11,17)=-2.31
ahyd(11,18)=-1.97
ahyd(11,19)=-1.02
ahyd(11,20)=-1.66
++++++++++++++++++
serine
ahyd(12,12)=-1.48
ahyd(12,13)=-1.37
ahyd(12,14)=-1.31
ahyd(12,15)=-1.48
ahyd(12,16)=-1.46
ahyd(12,17)=-1.94
ahyd(12,18)=-1.22
ahyd(12,19)=-0.83
ahyd(12,20)=-1.35
++++++++++++++++++
glutamine
ahyd(13,13)=-0.89
ahyd(13,14)=-1.36
ahyd(13,15)=-1.33
ahyd(13,16)=-1.26
ahyd(13,17)=-1.85
ahyd(13,18)=-1.85
ahyd(13,19)=-1.02
ahyd(13,20)=-1.73
++++++++++++++++++
asn
ahyd(14,14)=-1.59
ahyd(14,15)=-1.43
ahyd(14,16)=-1.33
ahyd(14,17)=-2.01
ahyd(14,18)=-1.41
ahyd(14,19)=-0.91
ahyd(14,20)=-1.43
++++++++++++++++++

glu
ahyd(15,15)=-1.18
ahyd(15,16)=-1.23
ahyd(15,17)=-2.27
ahyd(15,18)=-2.07
ahyd(15,19)=-1.60
ahyd(15,20)=-1.40
++++++++++++++++++
asp
ahyd(16,16)=-0.96
ahyd(16,17)=-2.14
ahyd(16,18)=-1.98
ahyd(16,19)=-1.32
ahyd(16,20)=-1.19
++++++++++++++++++
his
ahyd(17,17)=-2.78
ahyd(17,18)=-2.12
ahyd(17,19)=-1.09
ahyd(17,20)=-2.17
++++++++++++++++++
arg
ahyd(18,18)=-1.39
ahyd(18,19)=-0.06
ahyd(18,20)=-1.85
++++++++++++++++++
lys
ahyd(19,19)=0.13
ahyd(19,20)=-0.67
++++++++++++++++++
pro
ahyd(20,20)=-1.18

APPENDIX E

SAMPLE OUTPUT

The native contact pairs are:

2	18
25	53
57	163

Snapshot (interim report) every 5000 Monte Carlo timesteps.

TEMPERATURE OF THE SYSTEM = 0.340

Square of distance between adjacent c-carbons.

Radius of gyration squared.

Number of contacts between sidechains.

iterm=	R2=	AS2=	ENERGY=	native	any contacts
1	225	50.23	-302.2651	0	30
2	203	48.55	-294.1492	0	30
3	257	49.63	-298.5013	0	30
4	227	49.07	-301.3834	0	30
5	275	50.14	-306.7366	0	30
6	299	50.46	-304.1194	0	30
7	221	49.85	-303.1781	0	30
8	331	48.67	-294.3552	0	28
9	329	47.93	-294.4433	0	28
10	257	49.45	-291.8564	0	27
11	297	49.12	-299.2383	0	29
12	299	49.15	-299.5342	0	29
13	297	48.81	-298.7695	0	29
14	261	48.46	-294.4760	0	29
15	297	50.30	-300.5060	0	30
16	201	48.37	-292.5648	0	28
17	269	48.30	-293.5644	0	28
18	269	49.49	-298.5347	0	29
19	275	50.13	-305.4173	0	30
20	237	50.13	-285.0356	0	27
21	237	46.07	-288.0940	0	27
22	363	49.26	-298.0356	0	30
23	227	49.21	-293.2128	0	29
24	241	50.60	-297.5958	0	30

•
•
•

APPENDIX E

SAMPLE OUTPUT (CONT.)

FINAL CONFORMATION

	VECTOR1	VECTOR2	SIDE 1/2/3	HANDENES	
2	0 2 1	1 0 2	-1-1 1 -1-1 0 -1 0 1	-1	14 21
3	1 0 2	-2 0 1	1 1 1 1 1 0 1 0 1	-1	10 25
4	-2 0 1	1 0 2	-1-1-1 -1-1 0 -1 0-1	-1	10 11
5	1 0 2	2 -1 0	-1-1 1 -1-1 0 -1 0 1	-1	14 27
6	2 -1 0	2 0 -1	-1-1-1 -1-1 0 -1 0-1	-1	18 37
7	2 0 -1	2 0 1	-1 1-1 -1 1 0 -1 0-1	-1	16 37
8	2 0 1	2 1 0	1-1-1 1-1 0 1 0-1	-1	18 25
9	2 1 0	0 -1 2	-1 1-1 -1 1 0 -1 0-1	-1	8 9
10	0 -1 2	-2 0 1	1 1 1 1 1 0 1 0 1	-1	14 17
11	-2 0 1	0 -2 -1	0 0 0 0 0 0 0 0 0	1	8 17
12	0 -2 -1	-2 1 0	1-1 1 1-1 0 1 0 1	-1	6 21
13	-2 1 0	-2 -1 0	1 1-1 1 1 0 1 0-1	-1	16 37
14	-2 -1 0	-2 0 -1	-1 1 1 -1 1 0 -1 0 1	-1	18 35
15	-2 0 -1	-1 0 -2	-1 1 1 -1 1 0 -1 0 1	-1	18 29
16	-1 0 -2	-2 0 1	1-1-1 1-1 0 1 0-1	-1	10 21
17	-2 0 1	-1 2 0	1 1 1 1 1 0 1 0 1	-1	14 21
18	-1 2 0	1 2 0	-1-1 1 -1-1 0 -1 0 1	-1	16 21
19	1 2 0	-1 0 -2	1-1 1 1-1 0 1 0 1	-1	8 17
20	-1 0 -2	0 2 1	-1-1-1 -1-1 0 -1 0-1	-1	6 9
21	0 2 1	-1 0 2	-1 1-1 -1 1 0 -1 0-1	-1	14 27
22	-1 0 2	0 -1 2	-1-1-1 -1-1 0 -1 0-1	-1	18 27
23	0 -1 2	2 0 1	1-1-1 1-1 0 1 0-1	-1	14 17
24	2 0 1	0 -2 -1	-1 1 1 -1 1 0 -1 0 1	-1	8 17
25	0 -2 -1	1 0 2	1-1-1 1-1 0 1 0-1	-1	6 11
26	1 0 2	0 1 2	1 1-1 1 1 0 1 0-1	-1	18 21
27	0 1 2	1 -2 0	-1 1 1 -1 1 0 -1 0 1	-1	6 13
28	1 -2 0	-1 -2 0	1 1 1 1 1 0 1 0 1	-1	16 21
29	-1 -2 0	1 0 -2	-1 1 1 -1 1 0 -1 0 1	-1	8 9
30	1 0 -2	2 1 0	-1 1-1 -1 1 0 -1 0-1	-1	14 17
31	2 1 0	1 0 2	-1 1 1 -1 1 0 -1 0 1	-1	14 9
32	1 0 2	-1 -2 0	-1 1 1 -1 1 0 -1 0 1	-1	8 25
33	-1 -2 0	0 -1 2	1-1-1 1-1 0 1 0-1	-1	14 25
34	0 -1 2	1 0 2	1-1-1 1-1 0 1 0-1	-1	18 17
35	1 0 2	-1 2 0	1-1-1 1-1 0 1 0-1	-1	8 25
36	-1 2 0	0 2 1	0 0 0 0 0 0 0 0 0	1	18 27
37	0 2 1	0 1 -2	1 1 1 1 1 0 1 0 1	-1	10 29
38	0 1 -2	0 2 -1	-1-1-1 -1-1 0 -1 0-1	-1	18 17
39	0 2 -1	2 -1 0	-1 1 1 -1 1 0 -1 0 1	-1	6 19
40	2 -1 0	1 0 -2	-1-1-1 -1-1 0 -1 0-1	-1	14 25

•
•
•

APPENDIX E

SAMPLE OUTPUT (CONT.)

```
                .
                .
                .
  375  249    46.81 -292.8082     0    28
  376  269    45.55 -287.4545     0    30
  377  205    45.26 -290.7192     0    28
  378  299    49.93 -295.7486     0    27
  379  251    48.87 -292.7481     0    28
  380  285    48.30 -295.7492     0    29
  381  305    49.53 -295.7792     0    27
  382  275    47.54 -297.3956     0    27
  383  305    47.66 -296.4246     0    30
  384  285    48.34 -296.7784     0    26
  385  275    49.99 -305.2485     0    30
  386  117    48.92 -297.6013     0    30
  387  241    49.43 -299.3969     0    30
  388  299    49.99 -303.4559     0    30
  389  257    49.15 -298.2790     0    30
  390  275    49.46 -303.6329     0    30
  391  145    48.75 -300.4864     0    30
  392  373    48.91 -287.5453     0    29
  393  275    50.86 -301.0170     0    28
  394  275    50.16 -304.6649     0    30
  395  275    50.25 -302.6943     0    30
  396  293    50.86 -296.6948     0    28
  397  297    49.58 -298.8719     0    29
  398  299    49.58 -300.4898     0    28
  399  341    50.76 -296.8724     0    31
  400  269    49.22 -295.0204     0    28
 <E>= -295.6850     <E2>= 8.74568216D+04     CV= 2.71777422D+01
mean-square-end to end vector= 2.56595001D+02
<S2>= 4.85322037D+01
native contacts= 0.00000000D+00
 number of contacts= 2.84550000D+01

      fkink=      fend =     fwave=     frot=

      0.029328  0.133321  0.000000  0.001293

 ------------------------------------------------

  6   10797  140136   11818   10619   10528
  8   27659  102491   31519  101909   31348
 10   42315   42630   42626   42620   42721
 12   19949   45247   38505   40334   47439
 14  344543  344363  343647  345273  344759
 16  407038   70689   64827   63643   70601
 18  211817  211240  211463  211478  211935

  lenf  7*lenf  lenf-2 -nbgl  ngbl    78   546    70     6
```

APPENDIX E (CONT.)

SAMPLE OUTPUT (CONT.)

```
L-GLY, occupancy and side groups     72   546    70

************  contact map ************

    2and  4are inert      0.0000
**  3 and  7 are attractive   -12.5588
**  3 and 69 are attractive    -3.8824
**  5 and 15 are attractive   -11.2059
**  5 and 17 are attractive   -11.0588
**  5 and 19 are attractive    -9.3235
**  5 and 25 are attractive   -11.2059
**  7 and 69 are attractive    -8.7353
**  9 and 73 are attractive    -3.0000
** 10 and 72 are attractive    -9.9412
   11and 13are inert      0.0000
** 11 and 71 are attractive    -3.0000
   15and 17are inert      0.0000
** 17 and 25 are attractive    -3.0000
** 19 and 25 are attractive    -9.3235
** 28 and 32 are attractive    -9.3235
** 28 and 38 are attractive    -9.3235
** 32 and 38 are attractive   -11.2059
** 32 and 40 are attractive    -3.1176
** 45 and 53 are attractive    -9.9412

** 46 and 58 are attractive   -11.0588
** 47 and 61 are attractive    -7.4706
** 47 and 63 are attractive   -11.7059
** 52 and 70 are attractive    -9.9412
** 52 and 74 are attractive    -9.9412
** 55 and 75 are attractive    -3.0000
   61and 63are inert      0.0000
   70 and 74 residues are repulsive      0.8529
```

What is Claimed is:

1. Method of determining by a machine a three-dimensional structure of a protein or portion thereof including sidechains, the method comprising the steps of:

specifying a sequence of amino acid residues whose native tertiary structure is to be determined;

specifying local conformation preferences for respective residues of the sequence, and representing tertiary interactions between all pairs of sidechains;

specifying a temperature;

automatically generating a representation of an unfolded chain of the residues in three dimensions;

simulating in the machine folding of the chain and interactions between all pairs of sidechains, in accordance with said conformation preferences and said temperature, and producing a representation of a corresponding native tertiary structure; and

displaying the representation of the tertiary structure.

2. The method of claim 1 where the step of displaying includes the step of presenting the tertiary structure as a three-dimensional representation.

3. The method of claim 1 where the step of simulating includes the steps of stopping the simulating operation at an intermediate stage, specifying another temperature, and resuming the

simulating operation.

4. Method of determining a three-dimensional conformation of a globular protein utilizing Monte Carlo dynamics technique with asymmetric Metropolis sampling criterion, the method comprising the steps of:

specifying a sequence of amino acid residues of the protein;

generating a three-dimensional representation of an unfolded conformation consisting of an α-carbon backbone and sidechains in response to the specified sequence;

producing from the unfolded conformation, using said technique, successive likely conformations at a predetermined temperature according to the total energy of each conformation;

selecting from the successive likely conformations the lowest total-free-energy tertiary conformation which satisfies said criterion; and

determining the coordinates of the selected tertiary conformation for display.

5. The method of claim 4 where the step of producing includes the step of determining local conformational energetic preferences of the α-carbons.

6. The method of claim 5 where the step of producing includes the step of identifying spatially close pairs of sidechains in each conformation.

7. The method of claim 6 where the step of producing includes the step of simulating tertiary interactions between said spatially close pairs.

8. The method of claim 7 where the step of producing includes the step of determining the sum of the effective interaction contact energy between respective close pairs based on predetermined frequency of contact between said pairs.

9. The method according to claim 8 where the step of determining the effective interaction contact energy includes the step of scaling said energy to a selected lowest level by referencing average interaction contact energies of non-polar residues to a hydrophobicity scale.

10. A computer-based model for representing, in a three-dimensional cartesian coordinate system, a conformation of a protein or portion thereof, including the protein's α-carbon backbone and sidechains of finite surface area, as the protein folds from an unfolded sequence of amino acid residues to a folded tertiary structure, the model comprising:

a cubic arrangement of lattice sites disposed for framing the conformation;

the cubic arrangement being represented by unit vectors (±1,0,0), (0,±1,0), (0,0,±1), where the distance between adjacent lattice sites is unity; and where

each α-carbon occupies a lattice site located at a distance of √5 units from its adjacent α-carbon along a (±2,±1,0) vector or cyclic permutation thereof.

11. The model of claim 10 where said cubic arrangement is a 24-nearest neighbor lattice.

12. The model of claim 11 where each α-carbon is represented as occupying a central cubic lattice site plus six adjacent cubic lattice sites defining a surface of interaction of finite size, and each sidechain is represented as being embedded in the lattice and occupying a selected number of lattice sites located relative to said central site, the number of sites occupied by the sidechain being proportional to the number of sites defining the surface of interaction.

13. A computer-based system for determining a three-dimensional structure of a protein or portion thereof including sidechains, the system comprising:

input means for specifying a sequence of amino acid residues whose native tertiary structure is to be determined, and for specifying a temperature and local conformation preferences for respective residues of the sequence;

first memory means for storing the specified sequence, temperature, and conformation preferences;

second memory means having a stored program with routines for performing Monte Carlo dynamics simulation with asymmetric Metropolis sampling criterion and for representing tertiary interactions between all pairs of the sidechains;

processing means coupled to the input, and first and second memory means, and responsive to the specified sequence, temperature, and conformation preferences for, under control of the stored program, generating a first set of coordinates representing a conformation of an unfolded chain of the residues in three dimensions, determining a total free interaction energy from tertiary interactions between all pairs of the sidechains, simulating folding of

the chain at the specified temperature and in accordance with said conformation preferences and total interaction energy, and producing a second set of coordinates representing a native tertiary structure; and

display means coupled to the processing means for displaying the second set of coordinates depicting the native tertiary structure in three dimensions.

14. An apparatus for determining a three-dimensional structure of a selected protein including a plurality of α-carbons comprising:

means for storing a representation of a selected sequence of amino acid residues of the protein and an initial starting temperature value;

means for generating a representation of a cubic arrangement of lattice sites, including means for positioning adjacent sites a unit distance from one another and means for positioning a plurality of α-carbons on selected lattice sites, each α-carbon located a distance on the order of $\sqrt{5}$ from an adjacent α-carbon;

means for combining said generated representation of said cubic arrangement with said representation of said selected stored sequence;

means for producing, in response to said temperature and in accordance with said cubic arrangement, a representation of one or more folded, three-dimensional protein structures; and

means for comparing said produced representation of three-dimensional protein structure to a predetermined criterion and for selecting one of said produced representation for display only in response to a predetermined comparison result.

15. An apparatus as in claim 14 including means for interrupting said producing, for storing a new temperature value and re-initiating said producing.

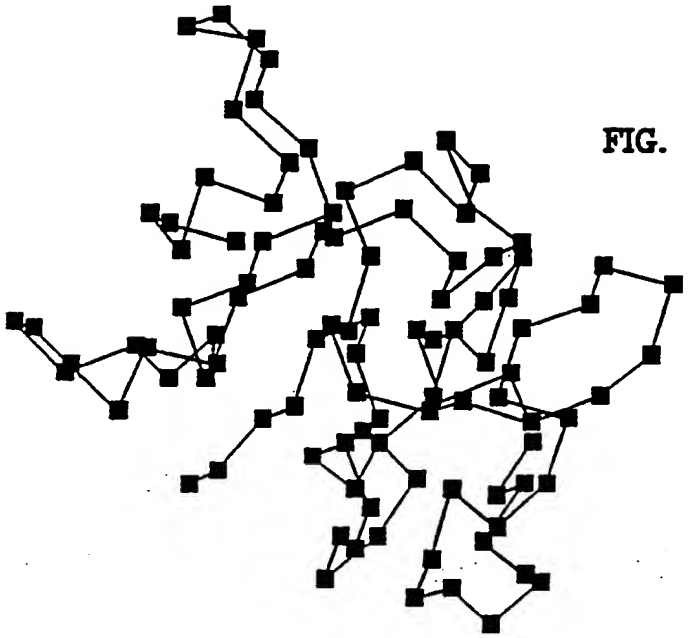
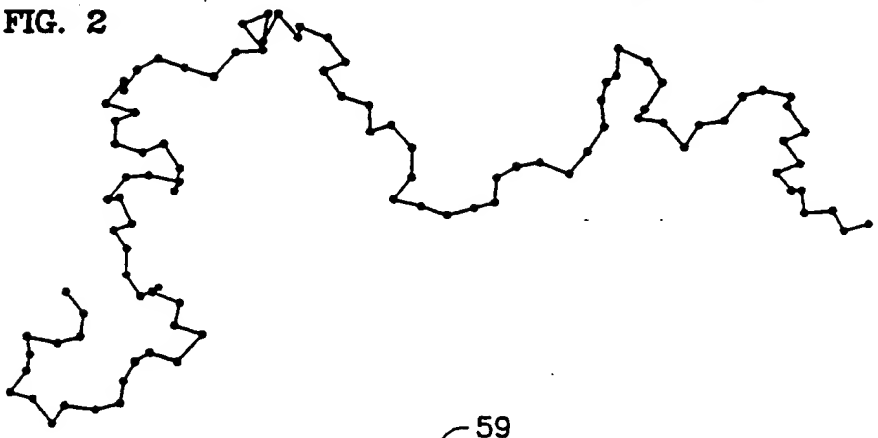


FIG. 1

FIG. 2



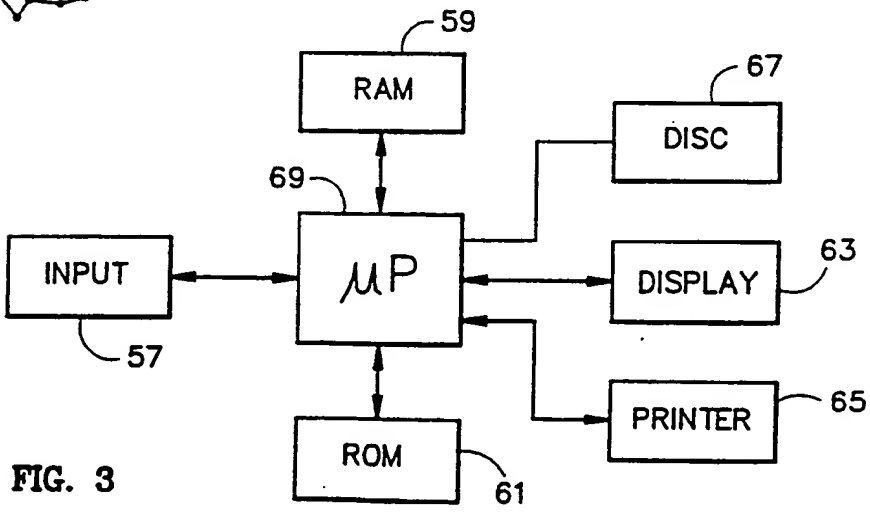


FIG. 3

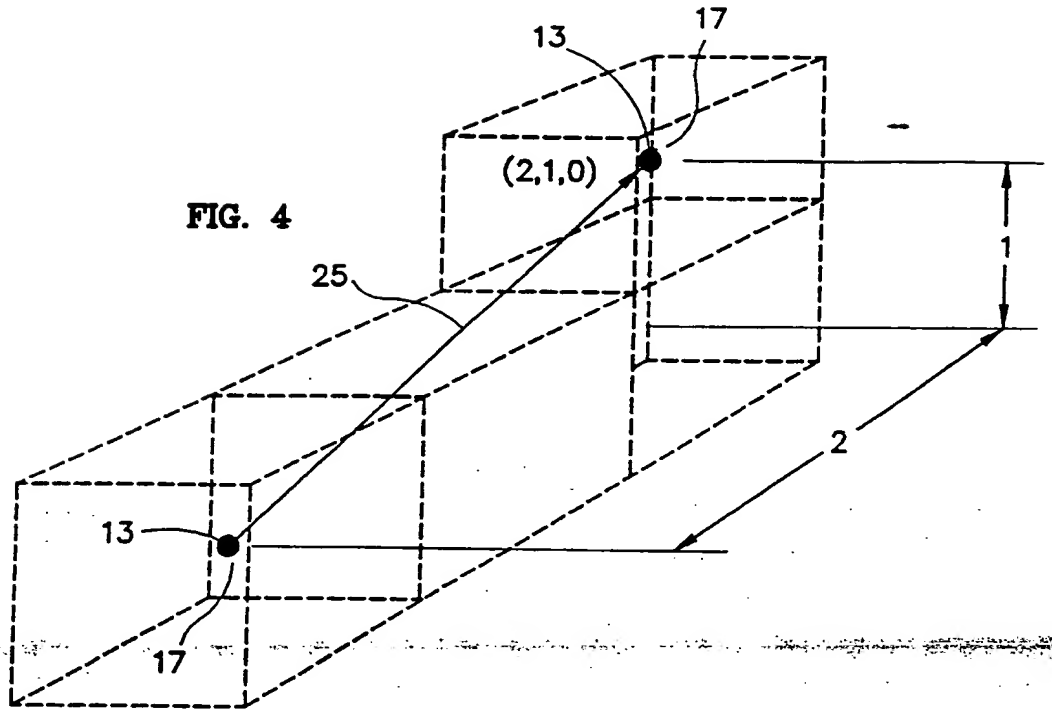


FIG. 4

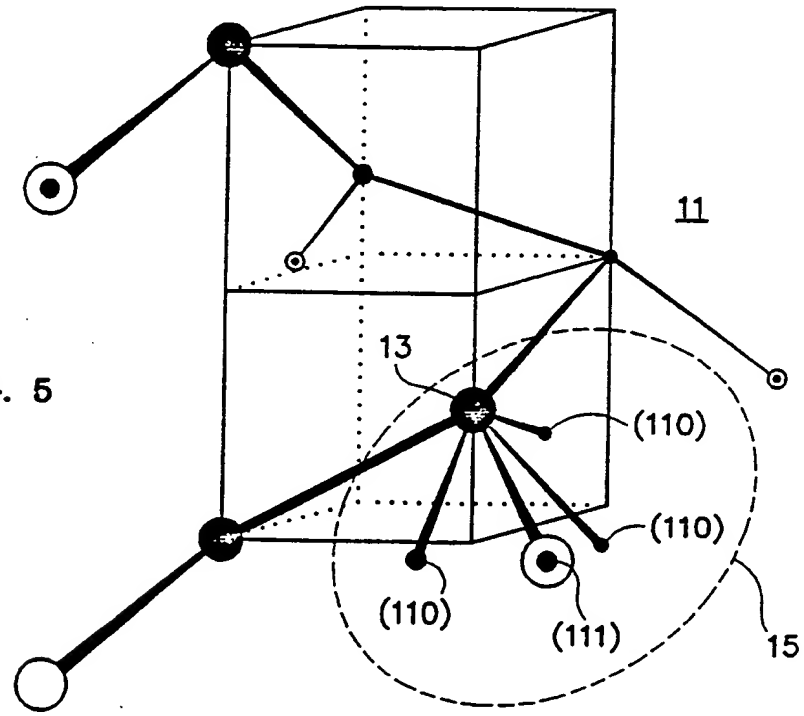
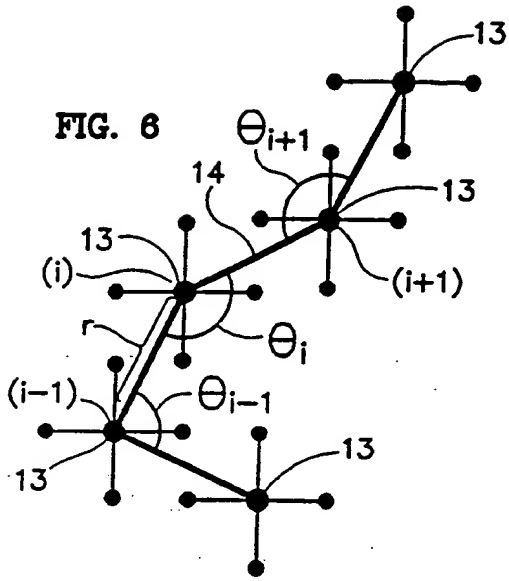


FIG. 5

FIG. 6



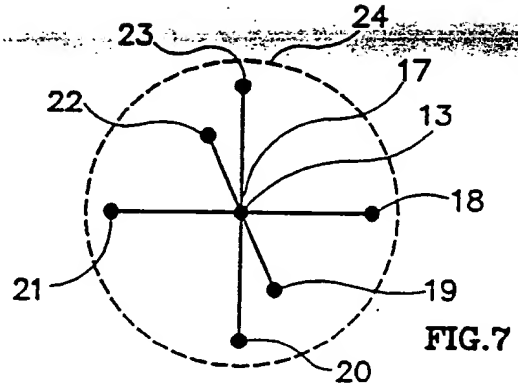


FIG.7

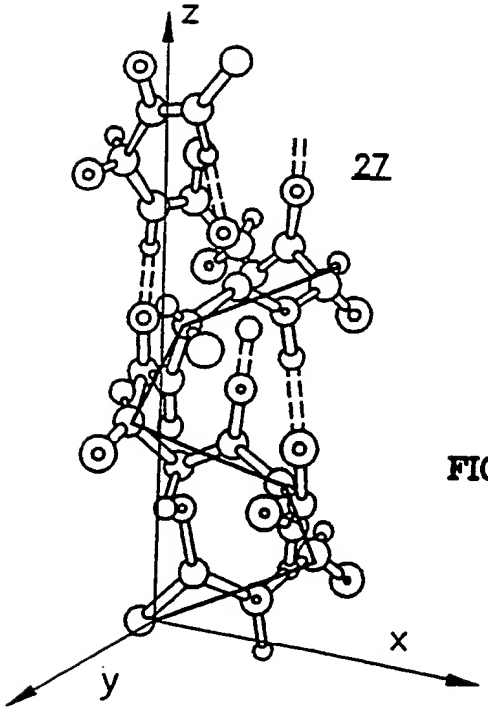


FIG. 8A

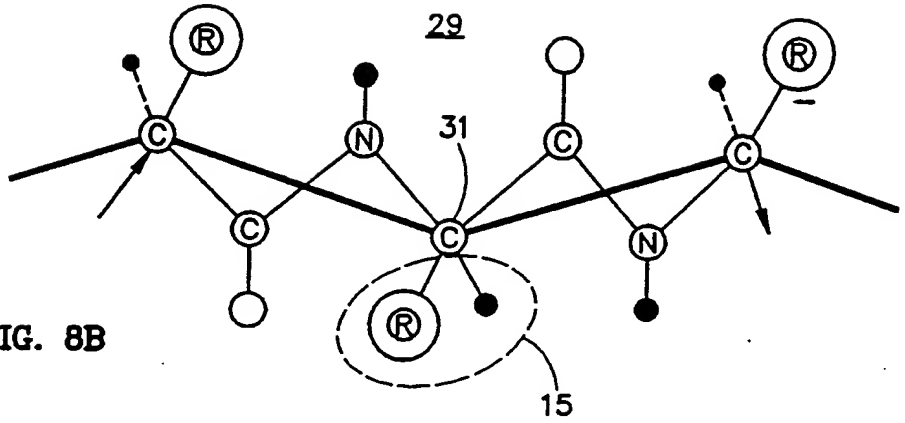


FIG. 8B

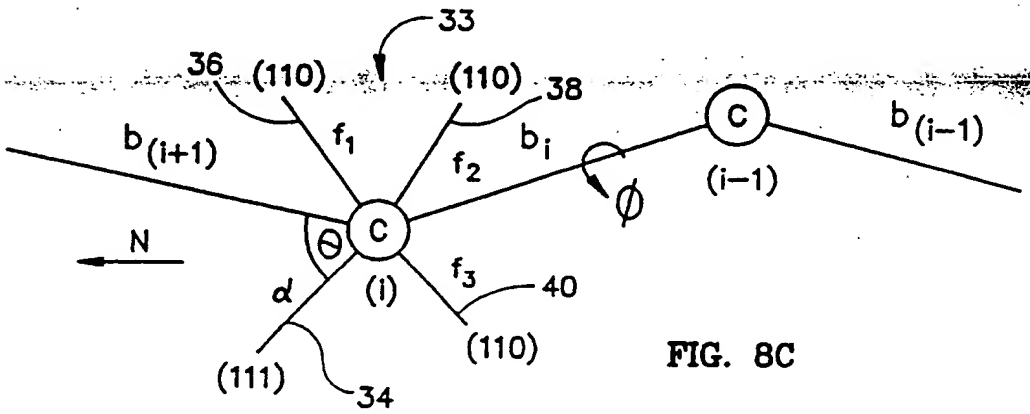


FIG. 8C

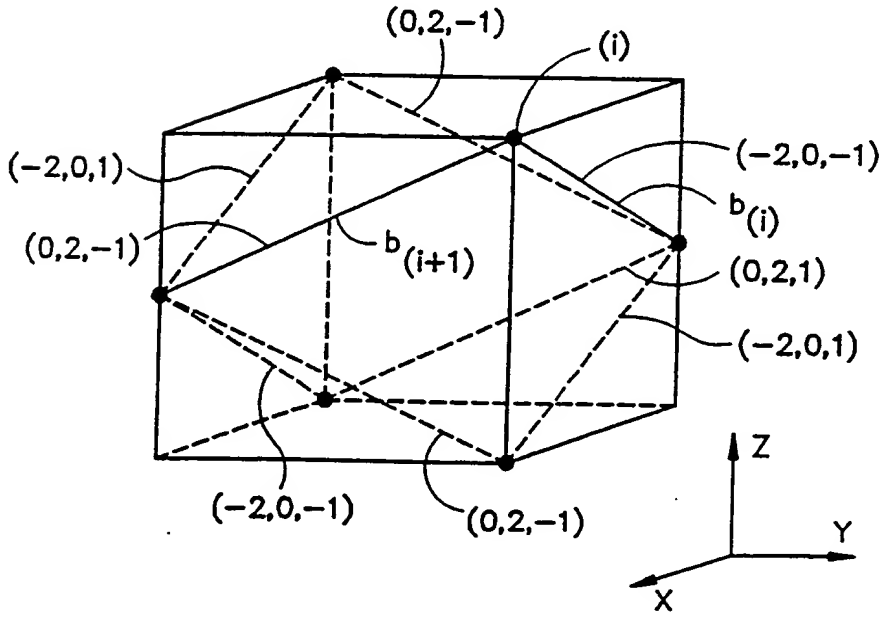
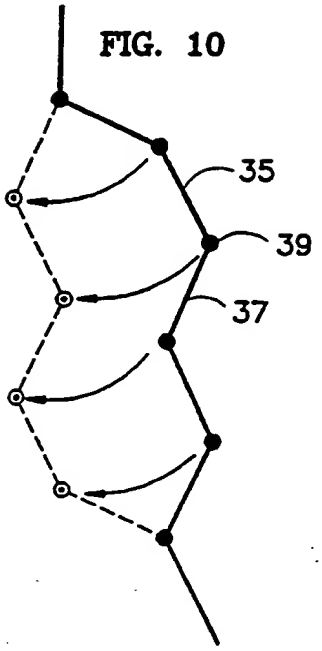
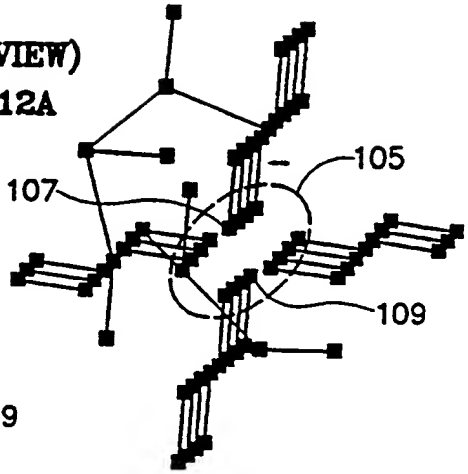


FIG. 9

FIG. 10



(SIDE VIEW)
FIG. 12A



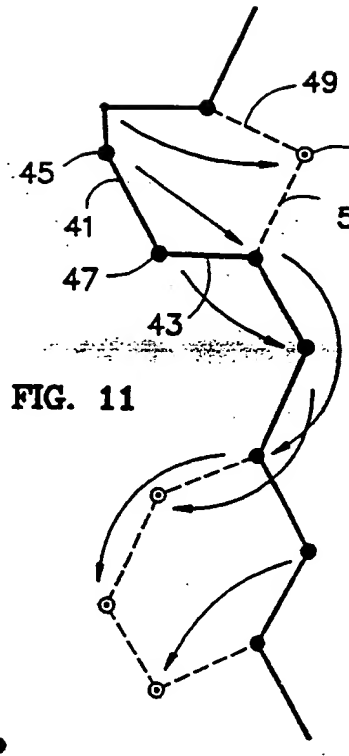
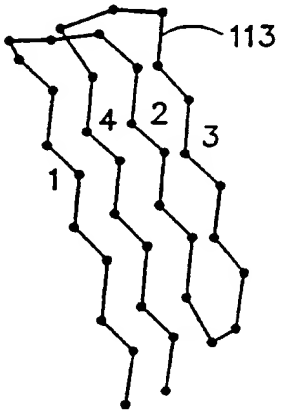


FIG. 11

FIG. 12D



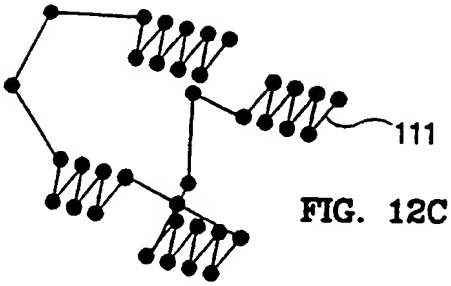
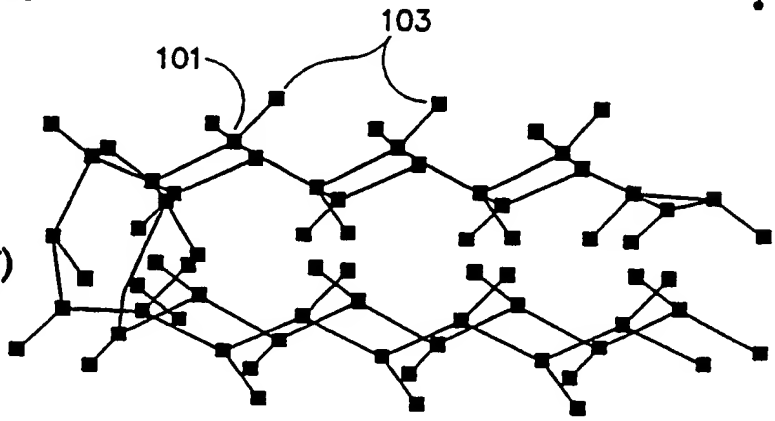


FIG. 12C



(TOP VIEW)
FIG. 12B

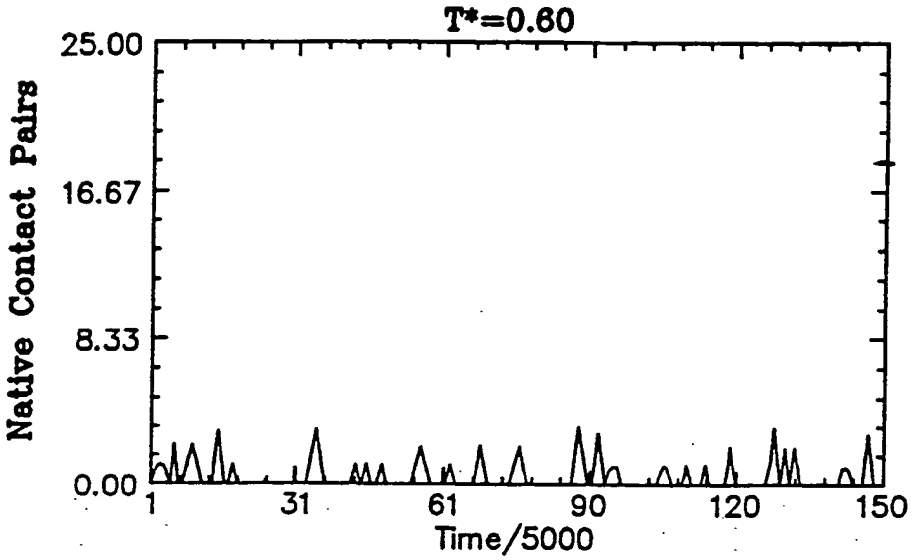


FIG. 13A

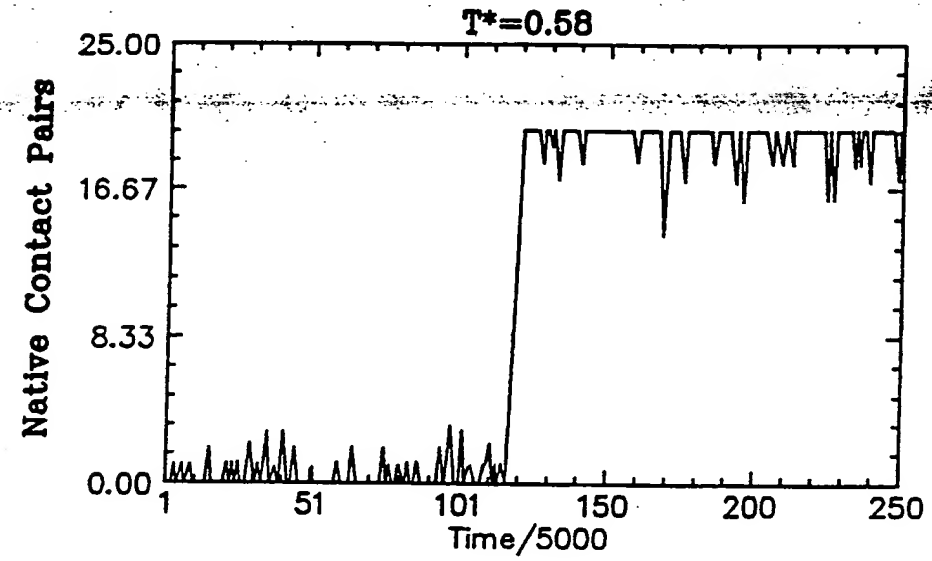


FIG. 13B

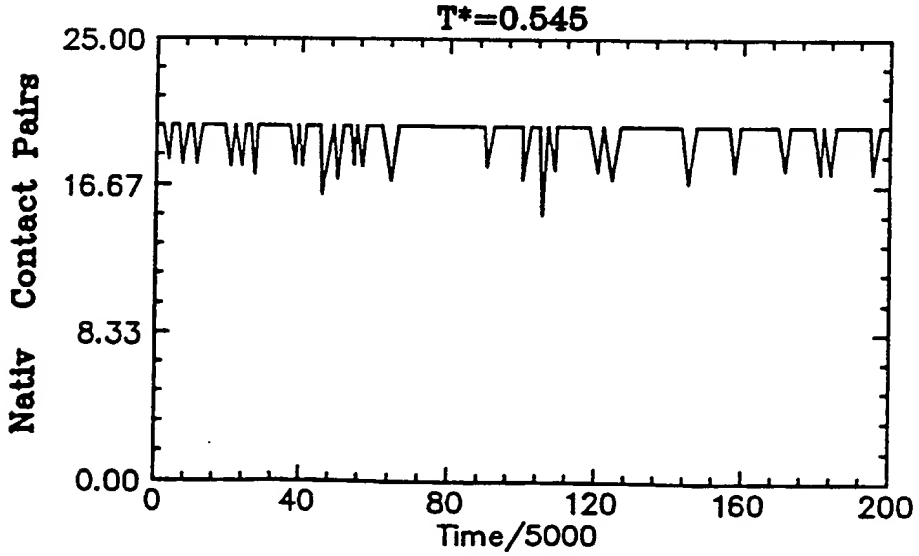


FIG. 13C

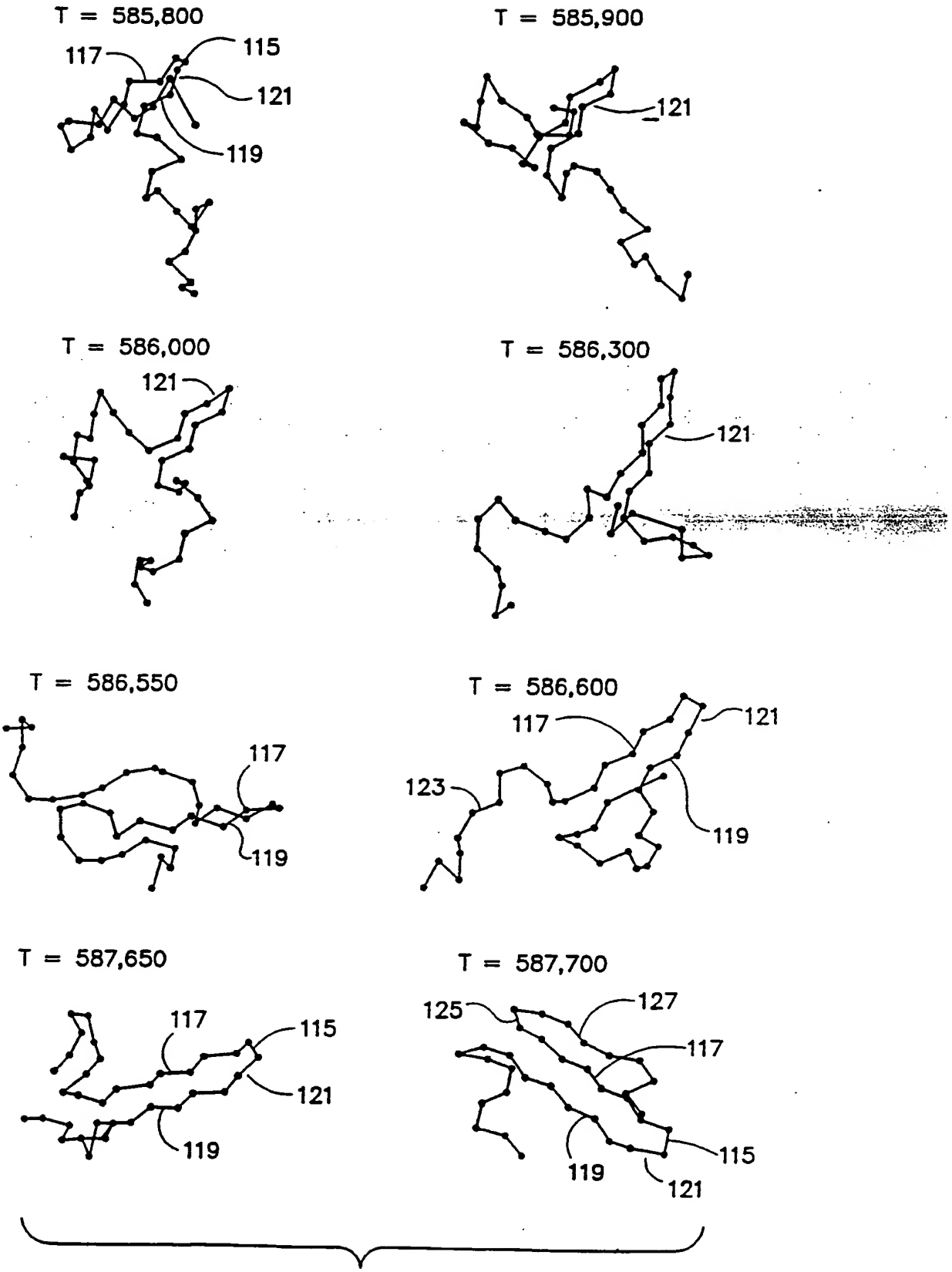

T = 585,800
117
115
121
119
T = 585,900
121
T = 586,000
121
T = 586,300
121
T = 586,550
117
119
T = 586,600
117
121
123
119
T = 587,650
117
115
121
119
T = 587,700
125
127
117
115
119
121

FIG. 14A

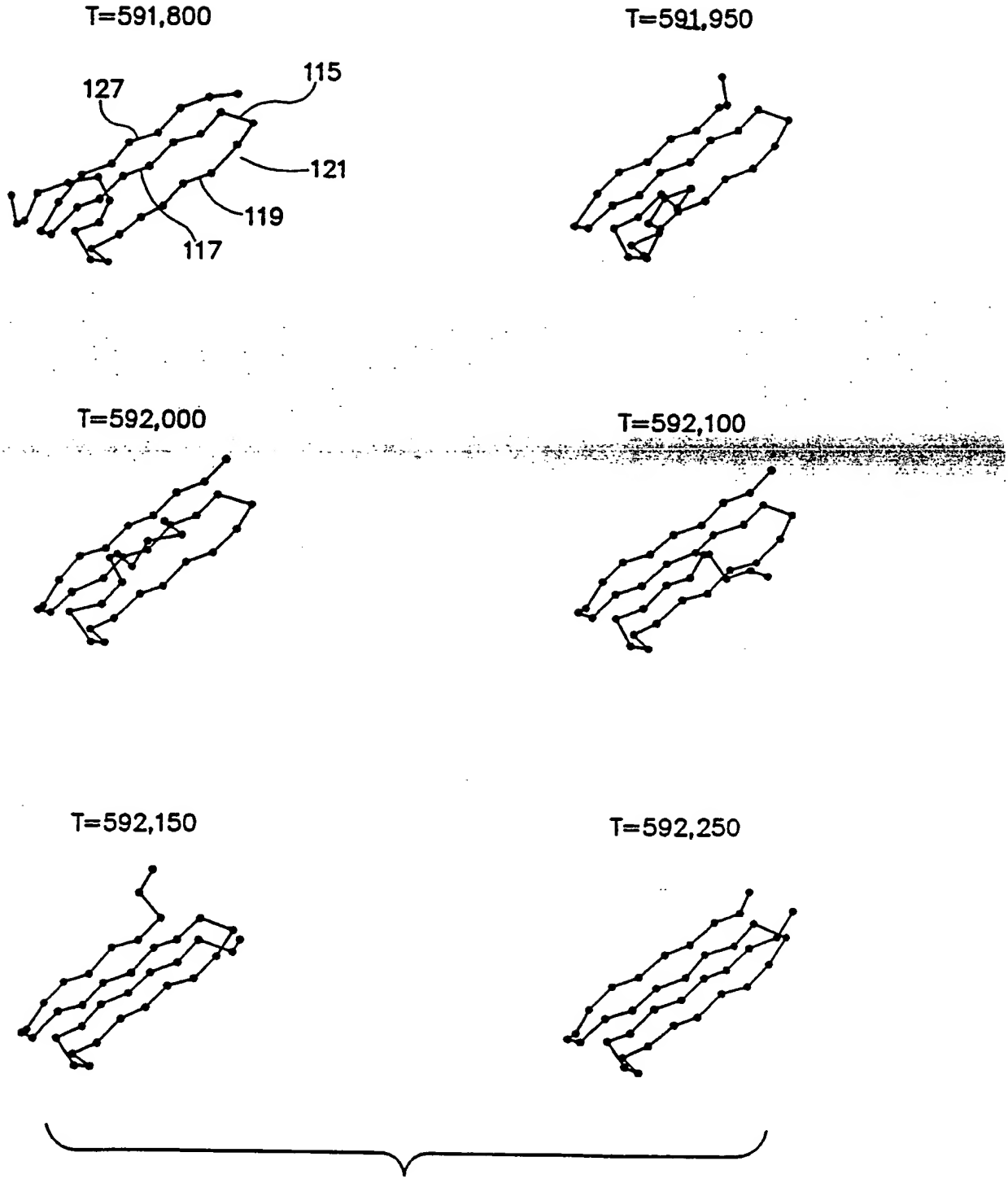

T=591,800
127
115
121
119
117
T=591,950
T=592,000
T=592,100
T=592,150
T=592,250

FIG. 14B

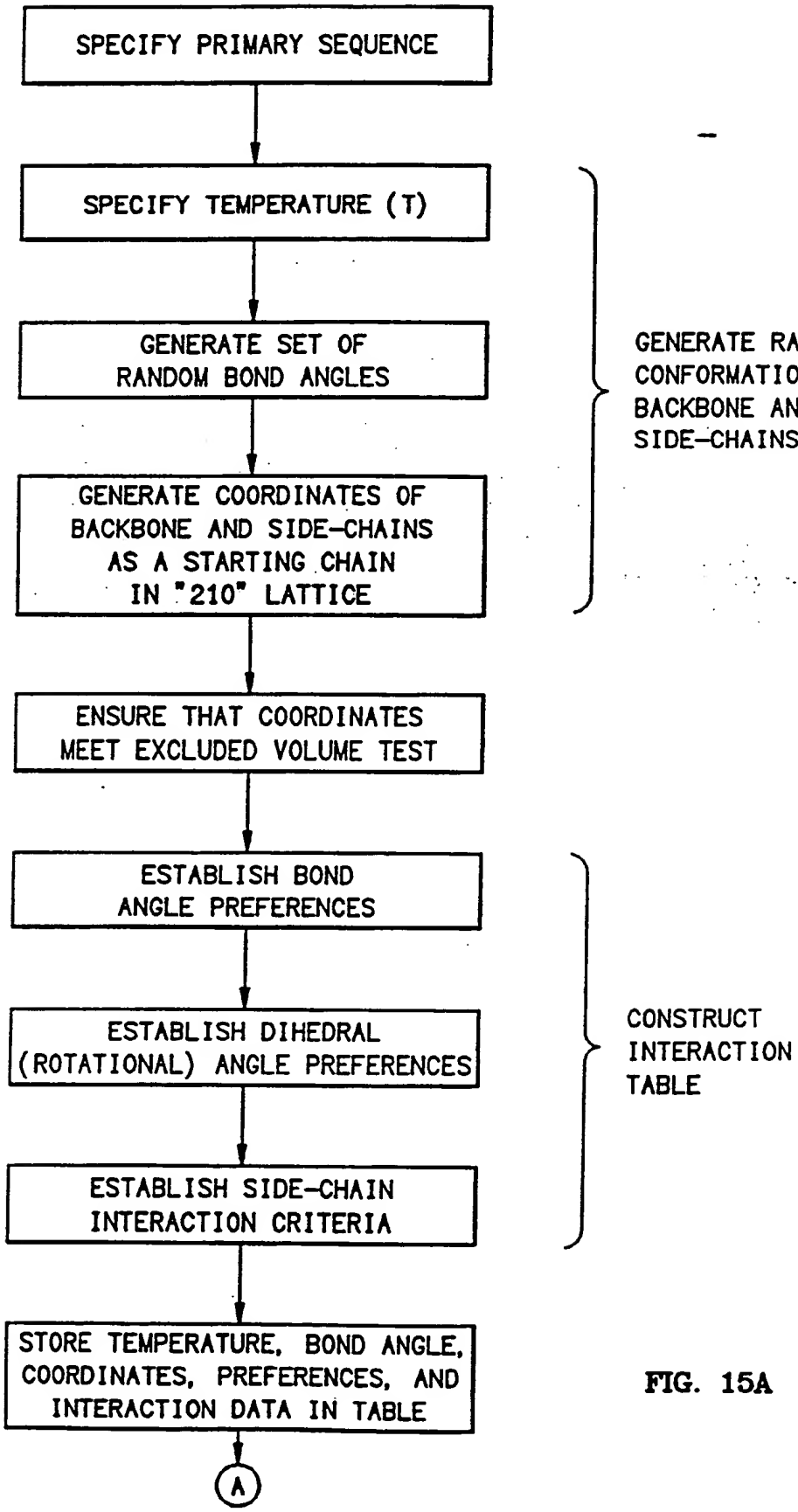

SPECIFY PRIMARY SEQUENCE
SPECIFY TEMPERATURE (T)
GENERATE SET OF RANDOM BOND ANGLES
GENERATE COORDINATES OF BACKBONE AND SIDE-CHAINS AS A STARTING CHAIN IN "210" LATTICE
GENERATE RANDOM CONFORMATION OF BACKBONE AND SIDE-CHAINS
ENSURE THAT COORDINATES MEET EXCLUDED VOLUME TEST
ESTABLISH BOND ANGLE PREFERENCES
ESTABLISH DIHEDRAL (ROTATIONAL) ANGLE PREFERENCES
ESTABLISH SIDE-CHAIN INTERACTION CRITERIA
CONSTRUCT INTERACTION TABLE
STORE TEMPERATURE, BOND ANGLE, COORDINATES, PREFERENCES, AND INTERACTION DATA IN TABLE
A

FIG. 15A

FIG. 15B

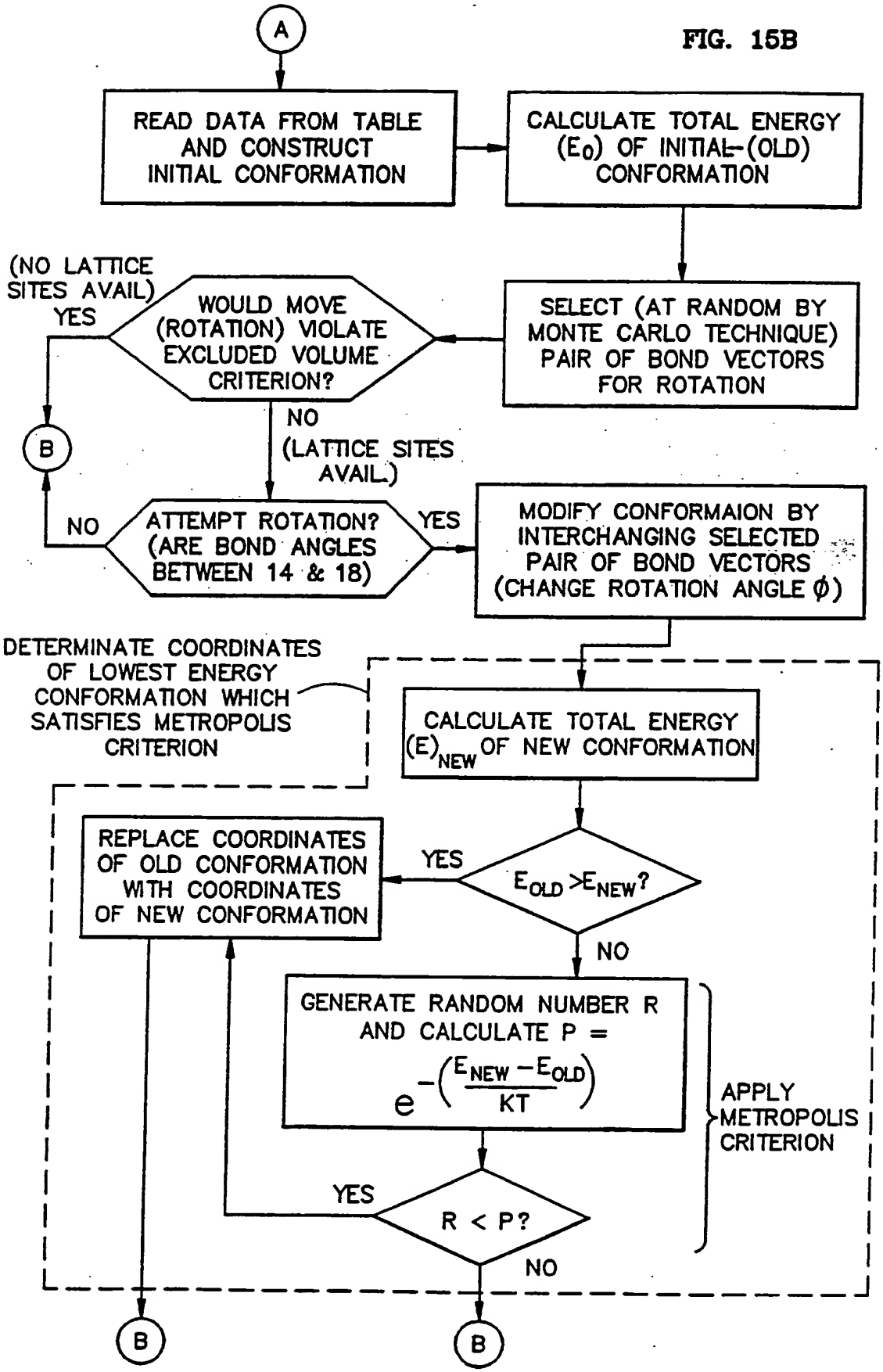
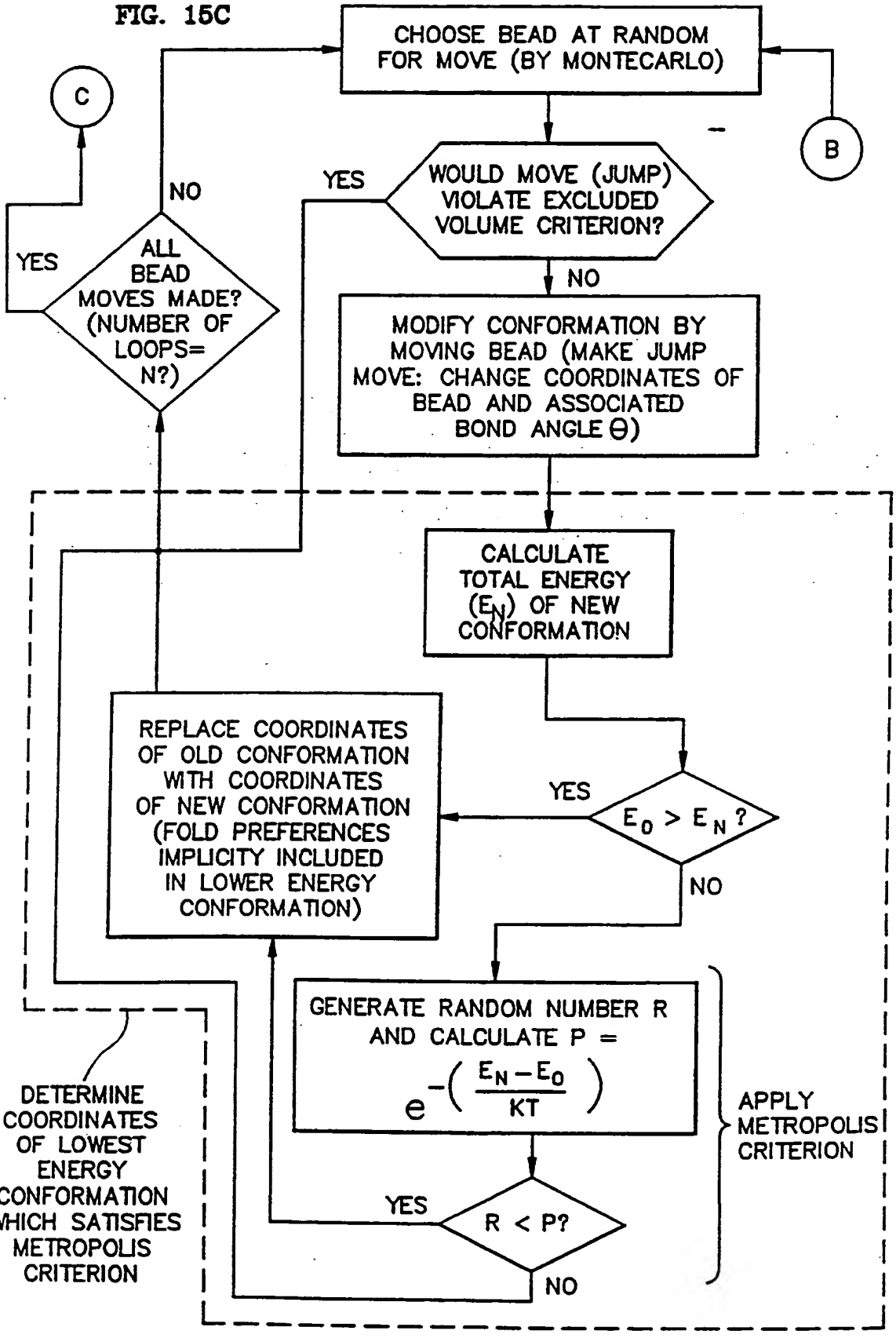

A
READ DATA FROM TABLE AND CONSTRUCT INITIAL CONFORMATION
CALCULATE TOTAL ENERGY (E_0) OF INITIAL-(OLD) CONFORMATION
SELECT (AT RANDOM BY MONTE CARLO TECHNIQUE) PAIR OF BOND VECTORS FOR ROTATION
WOULD MOVE (ROTATION) VIOLATE EXCLUDED VOLUME CRITERION?
(NO LATTICE SITES AVAIL)
YES
NO
(LATTICE SITES AVAIL.)
B
ATTEMPT ROTATION? (ARE BOND ANGLES BETWEEN 14 & 18)
NO
YES
MODIFY CONFORMAION BY INTERCHANGING SELECTED PAIR OF BOND VECTORS (CHANGE ROTATION ANGLE ϕ)
DETERMINATE COORDINATES OF LOWEST ENERGY CONFORMATION WHICH SATISFIES METROPOLIS CRITERION
CALCULATE TOTAL ENERGY $(E)_{NEW}$ OF NEW CONFORMATION
$E_{OLD} > E_{NEW}$?
YES
NO
REPLACE COORDINATES OF OLD CONFORMATION WITH COORDINATES OF NEW CONFORMATION
GENERATE RANDOM NUMBER R AND CALCULATE P = $e^{-\left(\frac{E_{NEW}-E_{OLD}}{KT}\right)}$
APPLY METROPOLIS CRITERION
R < P?
YES
NO
B
B

FIG. 15C


CHOOSE BEAD AT RANDOM FOR MOVE (BY MONTECARLO)
C
B
WOULD MOVE (JUMP) VIOLATE EXCLUDED VOLUME CRITERION?
YES
NO
ALL BEAD MOVES MADE? (NUMBER OF LOOPS= N?)
YES
NO
MODIFY CONFORMATION BY MOVING BEAD (MAKE JUMP MOVE: CHANGE COORDINATES OF BEAD AND ASSOCIATED BOND ANGLE Θ)
CALCULATE TOTAL ENERGY (E_N) OF NEW CONFORMATION
$E_O > E_N$?
YES
NO
REPLACE COORDINATES OF OLD CONFORMATION WITH COORDINATES OF NEW CONFORMATION (FOLD PREFERENCES IMPLICITY INCLUDED IN LOWER ENERGY CONFORMATION)
GENERATE RANDOM NUMBER R AND CALCULATE P = $e^{-\left(\frac{E_N - E_O}{KT}\right)}$
R < P?
YES
NO
APPLY METROPOLIS CRITERION
DETERMINE COORDINATES OF LOWEST ENERGY CONFORMATION WHICH SATISFIES METROPOLIS CRITERION

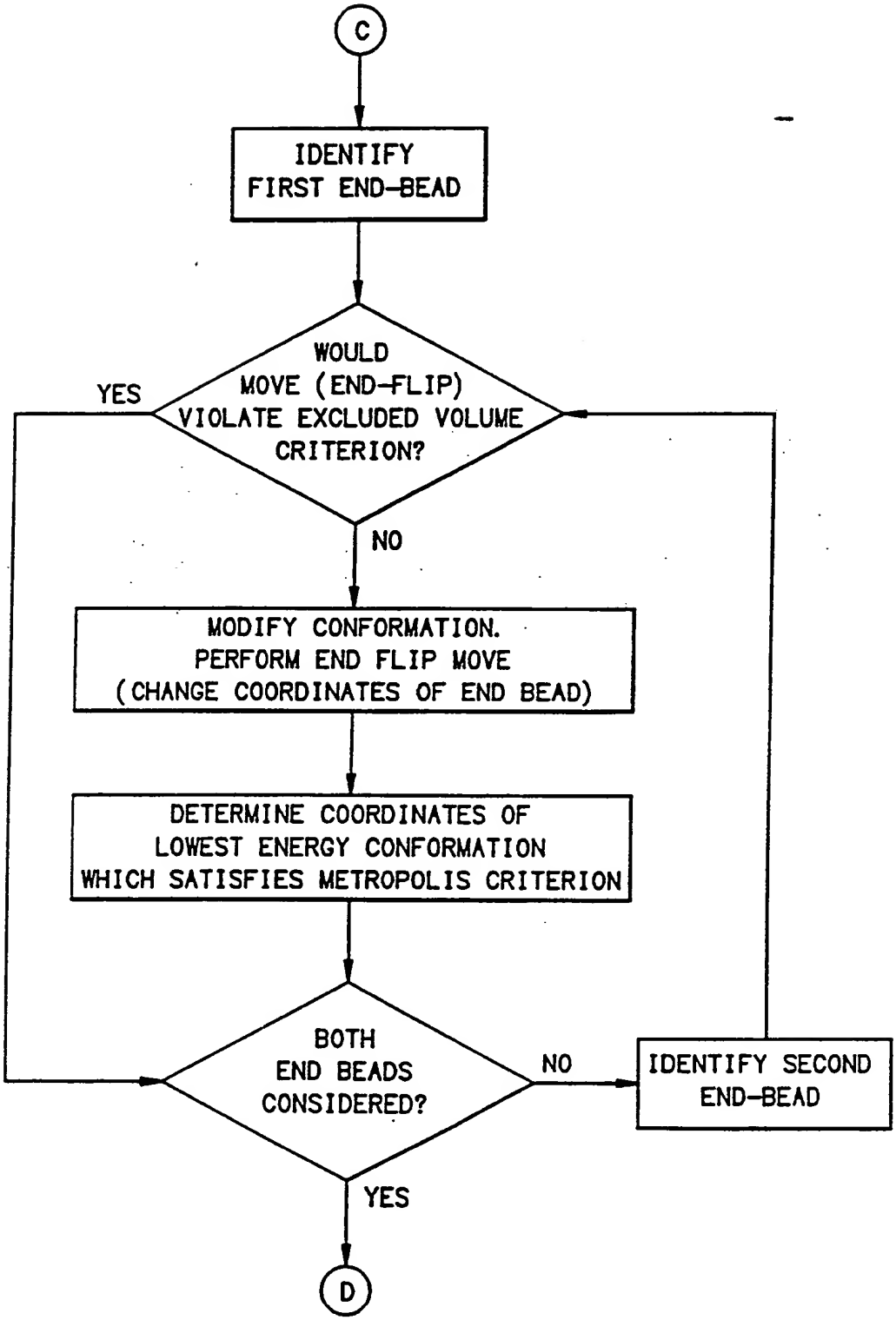
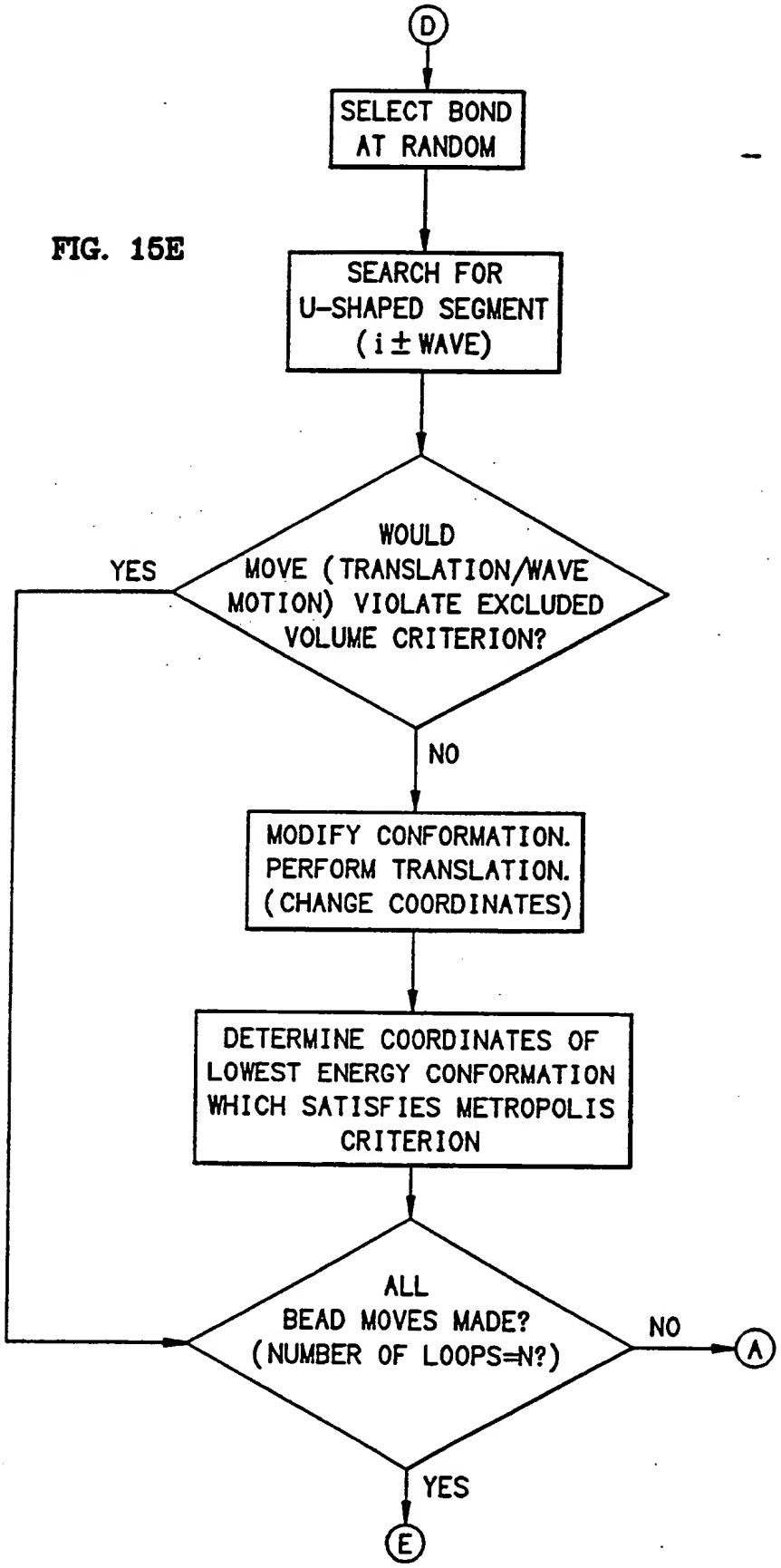

C
IDENTIFY FIRST END-BEAD
WOULD MOVE (END-FLIP) VIOLATE EXCLUDED VOLUME CRITERION?
YES
NO
MODIFY CONFORMATION. PERFORM END FLIP MOVE (CHANGE COORDINATES OF END BEAD)
DETERMINE COORDINATES OF LOWEST ENERGY CONFORMATION WHICH SATISFIES METROPOLIS CRITERION
BOTH END BEADS CONSIDERED?
NO
IDENTIFY SECOND END-BEAD
YES
D

FIG. 15D

FIG. 15E


D
SELECT BOND AT RANDOM
SEARCH FOR U-SHAPED SEGMENT (i ± WAVE)
WOULD MOVE (TRANSLATION/WAVE MOTION) VIOLATE EXCLUDED VOLUME CRITERION?
YES
NO
MODIFY CONFORMATION. PERFORM TRANSLATION. (CHANGE COORDINATES)
DETERMINE COORDINATES OF LOWEST ENERGY CONFORMATION WHICH SATISFIES METROPOLIS CRITERION
ALL BEAD MOVES MADE? (NUMBER OF LOOPS=N?)
NO
A
YES
E

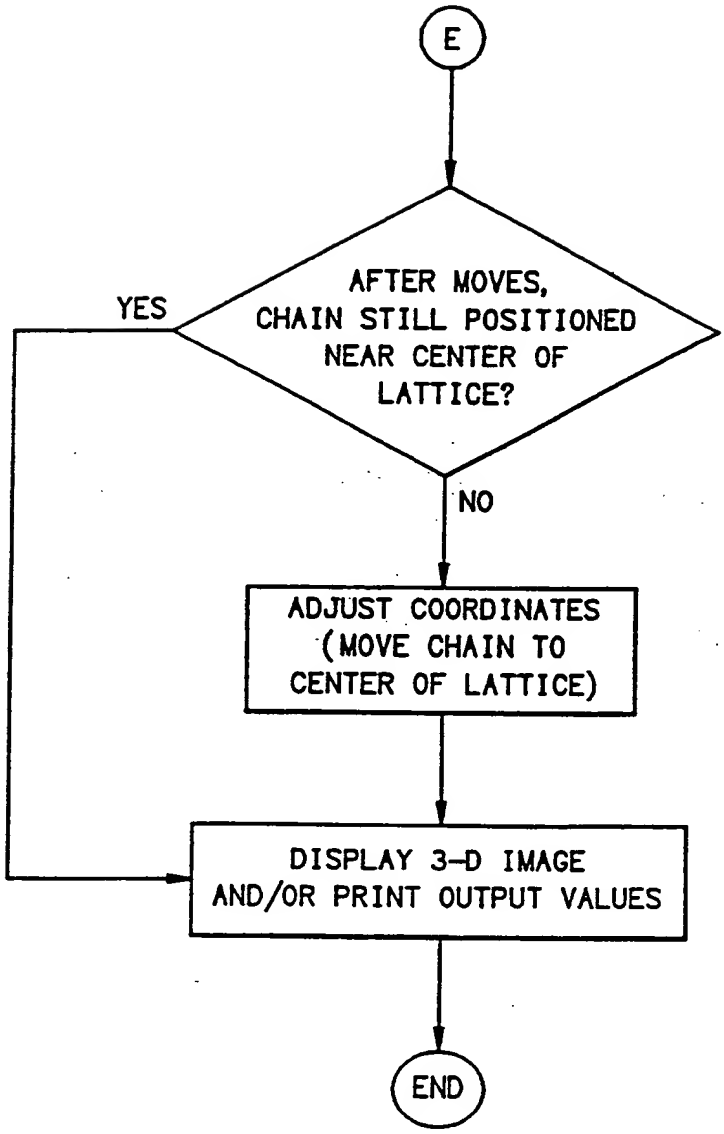

E
AFTER MOVES, CHAIN STILL POSITIONED NEAR CENTER OF LATTICE?
YES
NO
ADJUST COORDINATES (MOVE CHAIN TO CENTER OF LATTICE)
DISPLAY 3-D IMAGE AND/OR PRINT OUTPUT VALUES
END

FIG. 15F

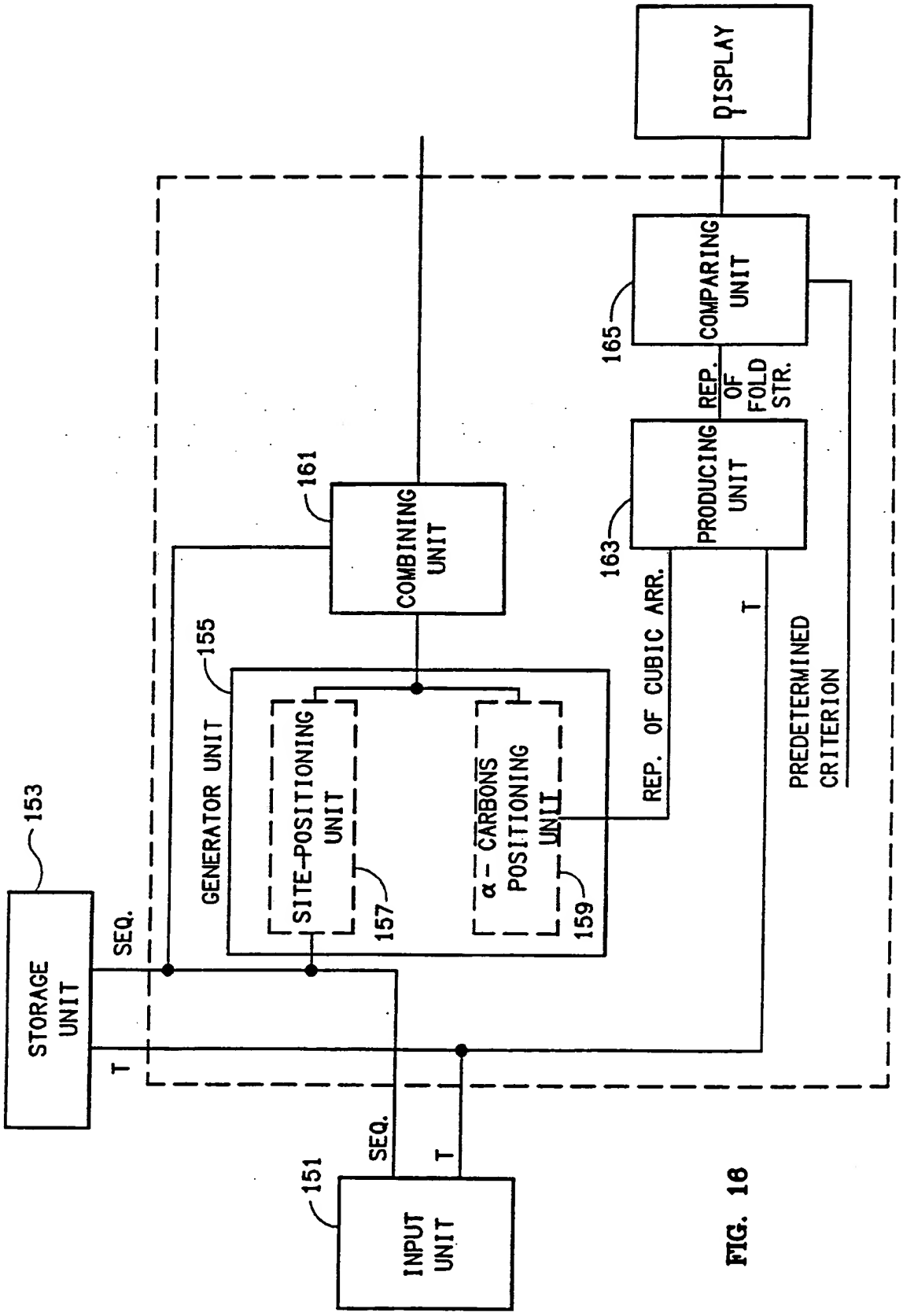

DISPLAY
COMPARING UNIT
165
REP. OF FOLD STR.
PRODUCING UNIT
163
REP. OF CUBIC ARR.
T
PREDETERMINED CRITERION
161
COMBINING UNIT
155
GENERATOR UNIT
SITE-POSITIONING UNIT
157
α-CARBONS POSITIONING UNIT
159
153
STORAGE UNIT
SEQ.
T
SEQ.
T
151
INPUT UNIT

FIG. 16

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/02786

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): G06F 15/46
USCL: 364/496

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US CL	364/496,497,498,578,579,200; 436/86,89

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US, A, 4,704,692 (LADNER) 03 NOVEMBER 1987	
A	US, A, 4,853,871 (PANTOLIANO) 01 AUGUST 1989	
A	US, A, 4,881,175 (LADNER) 14 NOVEMBER 1989	
A	US, A, 4,908,773 (PANTOLIANO ET AL) 13 MARCH 1990	
A,P	US, A, 4,939,666 (HARDMAN) 03 JULY 1990	
A,P	US, A, 4,985,827 (HAMANAKA ET AL) 15 JANUARY 1991	

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [3]
16 JULY 1991	16 AUG 1991

International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	for KEVIN J. TESKA Ngutho Nguyen NGUYEN DOC-HO INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (May 1986)

FURTHER INFORMATION CONTINUED FROM THE SEC ND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-15 because they relate to subject matter not required to be searched by this Authority, namely:

1) Claims 1-9 & 13-15 relate to "scientific & mathematical theories" (See PCT Rule 39.1(i)).

2) Claims 10-12 relate to "computer programs" (See PCT Rule 39.1(vi)).

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [2], specifically:

3. ☐ Claim numbers , because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.